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FUNDAMENTALS OF RADIATION CHEMISTRY

W. F. LIBBY, Ph.D.*

The basic phenomenon of radiobiology is the effect of radiation on molecules. The essential problem of classifying radiations is fairly well solved. The density of ionization produced by a radiation is described in terms of "ionization power." The most densely ionizing of the ordinary radiations is the alpha radiation which has a penetrating power through air in the order of 1-5 cm. To convert to tissue, divide by around 1000, that being the ratio of density of air to tissue. Alpha particles consist of the nuclei of helium atoms, and this emission is a result of the transformation of radium. Alpha radiation is followed, in the first instant, by a series of "children" radiations which are considerably more penetrating. Another type of radiation is the, so-called, beta radiation which consists of high-energy electrons. For equivalent energy, the range of the beta radiation is 100 times that of alpha radiation. One must consider, of course, the energy involved. A third type of radiation is the gamma radiation. This is an electromagnetic radiation in the general class of x-radiation, and is 100 times again more penetrating than beta particles. There is a fourth type of radiation known as "neutrons" which has no other accepted label. The penetration of neutrons is 10 times greater than that for gamma radiation. In all these cases, the penetration depends upon the energy. Of course, the penetrating power is an inverse function of the density of ionization, in that the total energy is equal to the range multiplied by the density of ionization.

Now, consider a difficult problem as far as you are concerned; namely, the explosion of a chain reaction bomb in which all of these radiations are produced. One must understand the nature of the molecular disruption which is caused by these radiations. X-radiation, gamma radiation, beta radiation, and alpha radiation all act by attacking the electronic structure of the molecule itself. Neutron radiation, on the other hand, acts solely through its attack on the atomic nuclei of the atoms involved in the molecule. This is the fundamental difference between the types of attack of these two groups of radiations. As you might expect, all the first groups of radiations, alpha, beta, gamma, etc., act by ionizing the molecule. Exposure to these radiations is characterized by the total integral ionization produced. A unit known as the Roentgen Unit is the amount of exposure which causes one e.s.u. of charge to be generated in one

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cubic centimeter of air. The Roentgen Unit, with which most of you are familiar, is used to characterize exposure to radiation; for it has been shown fairly well that, for certain types of effects, it is the net amount of ionization which counts and not the type of radiation. The point is much more doubtful insofar as neutrons are concerned because, as I have said, the neutron attack is of a different kind. Neutrons attack atomic nuclei; whereas, the other radiations attack the electronic structure which is the outer part of atoms. Ionization is the type of attack in which an electron is ejected from a molecule. For example, if water (which is the most abundant of all molecules in tissue) is irradiated with gamma rays, electrons are ejected from many H_2O molecules causing H_2O+ to form. If water is irradiated with x-rays, peroxide is produced. Hydrogen and oxygen are produced, but also peroxide. Now, of course, you know that peroxide is a bad material for the inside of a cell, and it is quite possible that part of the radiation damage to cells is due to the production of this extremely poisonous chemical within the cell body. While this is only a conjecture, it seems, on basic principles, the best approach to an understanding of radiation chemistry to assume that radiation damage is caused by the hydrogen peroxide which is produced by decomposition of water in the tissues. Recent findings involving the use of certain materials known to counteract peroxide, have borne out this theory to a certain extent. If injected prior to exposure to x-radiation, these materials have had beneficial effects. This line of research is likely to be of great importance in the event of atomic warfare.

The neutron consists of a bare nucleus which has no electronic structure. It is the atom with atomic number zero. It has no electrons, has the mass of a hydrogen atom, unit atomic weight, and is produced in great quantities during a chain reaction. It is the carrier of mass but, since it has no electronic structure, it has no charge. It does not attract, nor is it attracted by, electrons in the molecule. It interacts with the *nuclei* of atoms in the molecule. Now, there are two types of interaction. The first of these is simple collision which is characteristic of neutrons with high energy. High-energy neutrons are usually called "fast" neutrons. The other type of interaction involves slow neutrons, and I will speak of this type later on.

As I have said, fast neutrons interact by collision with atomic nuclei. Let us take the water molecule again. Suppose that this is the approximate shape of the molecule: H-O-H. Down in the center of each of its atoms is a tiny particle which constitutes the atomic nucleus. The diameter of the nucleus in about 10^{-12}cm., so there is a cross-sectional area of about 10^{-24} sq. cm. We speak of the cross-section for a neutron in terms of a unit known as the "barn". Now, an atom is in the order of magnitude of 10^{-16} sq.cm. in cross-sectional area; that is, the area of an atom is 100 million times larger than that of its nucleus. So, on the average, a fast neutron passes through 100 million ordinary atoms before it makes an impact. This means that it is quite penetrative. For example, half of a given intensity of neutrons passes through 10 cm. of tissue and reduces to 50% the intensity of any given beam of fast neutrons. So, if we are to shield the body from fast-neutron radiation, we must have several feet of water. Lead is much less effective than water—which brings up a point that is necessary to consider. For instance, if you play billiards, you know that the best way to slow down the cue-ball is to let it hit another billiard ball. If a much heavier particle is hit with a much lighter particle, the lighter particle (the cue-ball) will not stop. Instead, there is a deflection of the lighter object. The collision deflects the neutron from the original beam but does not take away its energy. There is very little ionization because of its velocity. The neutron bounces around and does its damage elsewhere. If, however, a neutron collides with a hydrogen atom, it loses about half of its energy and produces an ionizing particle. A fast neutron proceeding through 10 cm. of water has a fifty per cent chance of producing a "fast" proton by hitting and transferring its momentum to one of the protons, or hydrogen

nuclei, in the water molecule. The proton then proceeds along at a velocity comparable with that which the neutron had originally. But the proton is ionized, and the damage it causes is similar to the damage caused by alpha, beta, or gamma radiation. Please notice that the chances of producing ionization in this system are peculiar to the hydrogen atom. If a neutron hits the oxygen atom, the average transfer of energy is only something like 6%, since the oxygen atom is 16 times as heavy as the hydrogen atom. The neutron bounces back and there is very little transfer of energy. Consider heavy water in which the protons of ordinary water are replaced with deuterons; or rather, the ordinary hydrogen atoms are replaced with deuterium atoms which have twice the mass. Certainly, in using heavy water, there would be much less neutron damage to the body.

Neutrons can be slowed down by surrounding the source of fast neutrons—(all neutron sources are fast; that is, the neutrons born in any reaction have considerable velocity)—with water, the neutrons losing their energy by the process I have described. Please note that the neutron is not destroyed in this process. It simply collides with the proton, and the proton goes on and does the radiation damage. The neutron is still there.

There are nuclear reactions which are different from nuclear collisions. For example, consider the sodium in the body. A neutron, after it has suffered a good many collisions with water molecules, loses most of its energy and becomes a slow neutron with a velocity comparable with that of the atoms and molecules of water. A slow neutron will react, with considerable probability, with ordinary sodium, mass 23, to form a new type of sodium atom of mass 24. Perhaps you have read of some of the experiments at Bikini. Where the salt spray was radioactive, the bodies of the animals were intensely radioactive. The radioactivity, in this case, was very largely due to the reaction of slow neutrons. I know of researches where this type of effect (the radiation effect due to slow neutrons) has been exploited. Perhaps one of the elements which has the largest possibility for capturing slow neutrons is the boron isotope, mass 10. Boron, as you know, has two atomic weights, 10 and 11. Slow neutrons react to convert boron into an alpha particle and a lithium atom of mass 7, with high velocities. This reaction produces one of the most densely ionizing radiations known, at the site where the boron was originally located. About 10 years ago, Dr. Kreuger, at the University of Illinois, attempted to perform very localized radiation therapy by impregnating cells in this way.

These remarks illustrate the four types of radiation. The neutron is the most recently identified particle and there is a great deal to be learned about it.

In review, the neutron has two types of action both of which are nuclear in character. One is bouncing into nuclei which transfer its linear velocity. This is most effective when directed against hydrogen but has been done with other atoms. The neutron also reacts with nuclei to make radioactive materials which never before existed. The work which is yet to be done in this field is going to be exceedingly important. The question of whether you gentlemen understand this subject well enough to use it freely and easily is an extremely important one. I think the best advice is not to be afraid of it if you can handle x-rays properly. Most users regard it as that sort of thing. It is true that the neutron is bizarre in the way it acts, but it can be readily understood if you think about it a little. I think it would be desirable to set up an experiment with a neutron source, so that you could actually understand how neutrons behave. Neutron sources are readily procurable and can be made by mixing radium with beryllium powder. The little pellet then proceeds to pour out a stream of fast neutrons. Or, you might use the chain reaction of the pile at the Argonne Laboratories for both fast and slow neutrons. There is no substitute for experiment to understand what neutrons are like.

Now we might speak, for a moment, of the type of instrument used to measure these radiations. All of them are measured by virtue of the ionization which

they produce; so, all of the measuring instruments are essentially ionization detectors. The most elementary instrument is a photographic plate. The photographic plate apparently acts through ionization; or, at least, owes certain effects to ionization. The plates which are being developed now by Eastman Kodak and by Ilford in England are sufficiently sensitive to detect a single 10-Kv. electron. This development is of considerable importance in radiation detection. The great sensitivity of these plates makes them difficult to handle because they fog so easily. The photographc plate is approaching other types of detection in sensitivity and has great advantages, I think. Its handiness is a feature strongly in its favor. It is not linear in response. So, it is, at best, a qualitative instrument extremely useful in localizing effects in cells where radiations emitted by radioactive isotopes are used to localize certain chemical processes. This procedure is known as autoradiography and affords great opportunities with these new plates. I think this is the kind of thing which most of you know about and have actually done in your own laboratory work.

Radioactivity was discovered by means of photographic plates shortly after the discovery of x-radiation. X-radiation was conveniently measured by photographic plates. A sample of uranium was placed upon a photographic plate in an attempt to observe accurately natural x-rays. This was a logical idea, and it led to the immediate discovery of radioactivity.

Isotopes are available, at the present time, through the Atomic Energy Commission and, although their principal use has been in research, there have been a few therapeutic applications with phosphorous and iodine. The possibilities are so tremendous that they justify training M.D.'s and technicians in the technique on the campus, so that they will be able to make clinical and therapeutic applications during their practice. This training will help in the event of atomic warfare.

Now the next instrument is the Geiger counter, which was invented some ten years after the discovery of radioactivity. A crude model of it was used in 1908, but, even though the instrument is extremely simple in construction, the type in present use was not perfected until 1928. It consists of a cylinder with a wire through the center. The wire is in the order of one one-thousandth of an inch in diameter. The tube can be from one-quarter inch to one-half inch, up to three inches in diameter, and from one inch up to several feet in length. Some cylinders are six feet long, although six inches is a good average. Now, this Geiger counter is probably one of the most remarkable instruments in existence. It is certainly the most sensitive. It can detect, with high efficiency, a single electron of thermal velocity. It can detect a single charged particle, or a single electron that has so little energy as to be unable to ionize any other particle. The tube is filled usually with a special gas, although it will work with air. It performs best with argon or neon, with about 1/10 of an atmosphere of pressure and a little bit of ethyl alcohol. It can be produced by the thousands. A Geiger counter costs about $20.00 now. In volume, it could probably be produced for around $1.00, or less. A volume use is likely. There are in business now some twenty-four industrial companies selling these counters and the electrical equipment to go with them. A source of voltage is needed with a potential in the order of, say, 1500 volts. Such a voltage can be obtained from batteries, but it is somewhat easier to use a little box which looks like a radio set. A device to record the pulse is also needed. This mechanism takes the pulses off the wire, amplifies them and writes them down. The counter works quite simply and in this way: An electronic charge within the tube is in a strong field which repels it from the wall and drags it toward the wire in the center. As the charge proceeds toward the wire, the field gets stronger; because the field varies in the ratio of one over the distance from the wire. As it gets closer, it goes faster and faster until it reaches the velocity at which it can knock additional electrons out of the argon atoms. Then, each of those electrons can itself produce an avalanche. This occurs

until the entire wire is surrounded by a plasma of electrons of such density as to neutralize the field. This has two effects: First, the electrical pulse on the wire becomes uniform and independent of the frequency of the original radiation. The second effect is an amplification factor in the avalanche process. So, there will be a voltage on the wire of from several microvolts to 10 v. or 20 v. and, if you have had experience with electricity, you will realize that this is a large potential. Even though it is usually amplified by a couple of stages of amplification, it can be recorded directly. Geiger,, in his first experiments, simply hooked the wire to a string electrometer and photographed the electrons without any amplification. The disintegrations are usually written down with some kind of automatic recorder. The time the counter takes to write down a pulse is in the order of 100 microseconds. It can be jammed by bringing up a strong enough source, but it is rather difficult to jam. It can count at high rates, in the order of 10^3 per second. It jams at around 10,000 counts per second. This is important, because the Geiger counter is pretty sensitive. For example, one gram of radium will jam such a counter at about thirty feet. Now, a gram of radium is not too dangerous at thirty feet, although one would not want to stay there all day. It would not be harmful, however, to walk by it. The fact that such an exposure would jam the counter gives you an idea of its sensitivity and the ratio of damaging fluxes to its sensitivity range. This characteristic makes it too sensitive for most uses in radiobiology. So, a less sensitive instrument is needed for monitoring use. By dropping the voltage on this instrument and foregoing some of the amplification, it is converted into an ion chamber. An ion chamber need not have the cylindrical shape characteristic of the Geiger counter, but it can have this shape. By simply reducing the voltage on the instrument to around 150 volts, the sensitivity is greatly reduced and, at the same time, the range is increased. It will not jam so easily. These ion chambers may be in the form of pencils which can be carried in a coat pocket. They are quite reliable and, I believe, record roentgen units directly so that the overall exposure can be read at any time. The only difficulty is that they cost too much at present, but they are potentially useful. The ionization hazard in a room can be measured by so-called "monitoring" devices. The best of these, and the most sensitive, is the Geiger counter unless the fluxes are much higher than the counter's limit of sensitivity. Also, the Geiger counter is less rugged than some of the other instruments. An ion-chamber need not be vacuum tight. Therefore, a rugged machine with heavy insulators can be built which can be banged around. These scanning meters are purchasable.

The Atomic Energy Commission supplies isotopes and certain isotopes can also be obtained from commercial companies. The U. S. Radium Corporation sells radium and polonium. The latter is a very nice source of pure alpha radiation and has a half-life of about six months. It takes about a year or two for it to die off too much to be useful, and it provides a localized radiation suitable for the study of radiobiology. Radium has the advantage of building up a series of "children" which contain beta and gamma rays. If you want those, then it's all right. I think that this kind of thing can frequently be done about as well by the use of high-energy x-rays as by the use of radioactive isotopes.

For neutrons, the best thing to do is to go to a chain-reacting pile if you want to study radiobiology, but you can get significant intensities from other sources. Very little of this has been done.

Most isotopes are available by purchase from the Atomic Energy Commission, and I think that prices on most of them would be called nominal. There is a charge for people's salaries and packaging costs, but the isotopes themselves are not charged for. For cancer use, even the handling charge is eliminated.

Isotopes are measured in curies. A curie has come to mean the amount of radioactive isotope which gives a certain rate of disintegration, the rate of disintegration of one gram of radium. So, if an isotope has a lifetime of, say, 12 years, a neutron spent obtaining it is ten times

more effective than if spent producing another isotope with a lifetime of 120 years, or ten times less effective than if used to produce an isotope of 1.2 years of life. It is the neutrons that cost money: A neutron has a certain life, and a certain amount of plutonium can be produced by it. Radio-iodine or Carbon-14 or a host of other isotopes can be made. But whatever is made costs a neutron, and one must decide how the neutron is to be spent. Insofar as medical uses are concerned, I think a lifetime of about a year is all that is necessary. Some isotopes are much longer-lived. Carbon-14 is an example. It has a 5700-year half life. It is a carbon isotope made by the irradiation of nitrogen with slow neutrons. As radiocarbon is available in great abundance, the opportunity exists of producing all drugs in radioactive form. Tritium is a radioactive isotope with a half-life of about twelve years, so it is inexpensive in terms of neutrons. Tritium is going to be extremely useful, apparently, although Carbon-14 is overshadowing it at present. However, tritium will compete before long for the reason that it is cheaper. For many purposes, a biological can be marked about as well with hydrogen as it can with carbon. Certain hydrogen atoms in the molecules are probably not removed in metabolic processes where they are used. Tritium marking is so cheap that the following projects would be conceivable: The water of a small lake five miles across could be marked so that it could be followed for twenty miles, or further. To put this another way, suppose Standard Oil of Indiana wanted to distinguish its gasoline from all other brands of gasoline. If the Atomic Energy Commission granted tritium for this purpose, it could be done for about $2,000.00 a year. That is possible with tritium. A tremendous dilution factor is available by using this radioactive hydrogen. It really makes a unique isotope. Consider the problem of metabolism of odors and what happens to the molecules which cause a smell. It is well known that the number of molecules involved in some odors is very small indeed. It is quite possible, for instance, that by smelling perfume made radioactive with tritium the metabolism of odors could be traced. Such an experiment involves a dilution factor which is inconceivable with any other isotope. Experimentation becomes quite practical with this inexpensive, very interesting substance.

We are working with the Argonne National Laboratory, as a matter of fact, on what we call a "horse farm". This is a misnomer because we have not yet grown a horse, but the objective of this farm is to develop a balanced economy using radioactive atoms. To date, a considerable quantity of radioactive algae and larger plants have been produced. Some objectives right now are sugar beets and tobacco. These substances contain a large number of interesting chemicals including the vitamins. The attempt is to build up fodder for the support of an animal colony. This project is supported by the Atomic Energy Commission and is directed by Dr. Norbert J. Scully. It is assumed that these products will be useful. There has already been considerable interest in the algae. You see, these plants are uniformly radioactive. All the sugars, all the amino acids; everything in them has the same chance of becoming radioactive. There is no single position of a molecule which is more likely to become radioactive than any other. One could imagine—I say imagine—diagnostic uses. Give a patient a lump of radioactive sugar and his breath becomes radioactive. The appearance of radioactivity in the breath and in the urine might prove to be a unique test. Whether it would be useful diagnostically, I do not know. I do know that it would be very simple. I suspect strongly that it would not be dangerous at useful levels.

The next rather interesting possibility is what we call isotope horse-farms. I would like to have you come out and visit the farm at Palos Park sometime so that you could see the plants and, perhaps, some animals on the radioactive farm. If anyone here has a use for such products in his research, I hope you will discuss the problem with Dr. Scully or me.

THE APPLICATION OF ISOTOPE TECHNIQUES TO BIOLOGICAL PROBLEMS

A. ROBERT GOLDFARB, Ph.D.*

Introduction

It has been recognized that in a study of metabolic processes "tracer" atoms or groups are of great utility. Thus, early in the studies of fat metabolism Knoop fed omega phenyl fatty acids to experimental animals and determined the character of the phenylated compounds which he was able to isolate. The interesting discovery was made that, when he fed the phenyl fatty acid containing an even number of —CH_2— groups he isolated exclusively benzoic acid (as hippuric acid) and when he used fatty acids containing an odd number of — CH_2— groups he obtained exclusively phenylacetic acid (also as its conjugate with glycine). From these experiments was evolved the "beta oxidation" hypothesis for the intermediate metabolism of fatty acids. It could be argued in this particular case that the validity of this experimental data was open to the serious objection that the compounds used were not "physiological" in that the large size of the terminal phenyl group could easily distort the metabolic process through its alterations of the physical and chemical properties of the fatty acids.

With the developments in physics and physical chemistry that led to the separation, in bulk, of relatively large amounts of isotopes, they became available for use by biologists, biochemists and physiologists. Shortly after the discovery of isotopes, Hevesy published the first studies of intermediate metabolism using radioactive isotopes. Later, in the early 1930's, Schonheimer and Rittenberg utilized the stable isotopes deuterium and N^{15} which had been made available to them by Urey.

The application of isotopic atoms as tracers is based on two assumptions:

1. That living organisms cannot distinguish between isotopes. Thus far this has been found true of all elements except deuterium (H^2) which is toxic to organisms as will be shown later.

2. That the isotopic concertrations in tissue is constant. This has been quite well established for the stable isotopes.

Requirements of Tracer Studies

A. The initial concentration of tracer element that is being used must be sufficiently great so as to withstand dilution effects. To make this clear consider a simple example: It is desired to study the biological exchange between P^{32} as phosphate in the bound phosphorous of a given tissue. If from earlier work it is known that the total phosphorous in the tissue is about 100 mg., and 0.1 mg. of P^{32} is added, a dilution of 1:1000 will result. If now the activity of the P^{32} is 10,000 c/m (counts per minute) the specific activity of the resulting phosphorous will be $1/1000 \times 10{,}000$ or 10 counts per minute per milligram. Given now that 5 mg. of P are to be used for an assay, the total count will be 50 c/m. For sufficient accuracy the count should be at least 10 × the background count (the background count being that obtained from a counting device which is due to contamination of the equipment and to cosmic radiation). As a rule the background count will be in the neighborhood of 20 c/m and so a sample must be obtained having at least 200 counts per minute. To obtain such a result either 0.4 mg of the P^{32} is used or 0.2 mg of P^{32} having an activity of 20,000 c/m.

B. The isotope must, under non-metabolic conditions, remain bound in a stable manner. For example, in such structures as —OH*, NH_2*, CO—CH*, the H* exchanges rapidly with water and cannot be used to label a group for studies. However, in the case of — C — CH* — C — C and C_6H_5*, the H* cannot exchange under metabolic conditions.

C. As indicated earlier the presence of a labeled atom must not interfere with normal metabolic processes. With radio-

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active isotopes the overall concentration should be sufficiently low so as to minimize radiation effects. With stable isotopes in several cases the concentration has an important bearing on the biological activity. For example, in carrying out experiments in the presence of heavy water, it is known that, if the concentration of Deuterium is too high respiratory and fermentation reactions are inhibited or poisoned. From a study of this problem it has been determined that the ratio D/H should be less than 1/5.

D. In the use of radio-isotopes the half life of the isotope should be sufficiently long so as to permit carrying out the experiments. It is usually considered that at 10 half lives the concentration of isotopes is negligible ($1/2^{10}=1/1024$). As an example of the importance of this concept consider work with radioactive C^{11} which has a half life of 20.5 minutes and in 3½ hours its activity is 0.1% of the activity at the start of the experiment. This can be compared with C^{14} of the half life of 5,000 years.

Introduction to Studies

In the studies of intermediate metabolism two questions are raised, namely, (1) are the administered materials absorbed and utilized and (2) are they localized? The practical problem of isolating and analyzing all of the metabolite is in most cases impossible. However, given a very sensitive label the problem becomes exceedingly simple. In general, the procedure is reduced to administering the labelled material and after suitable time the tissue or tissues under examination are withdrawn and examined for the presence of the isotope. If the isotope is present, absorption is proved. As an example in one of the first studies on absorption, Hevesy[1] studied the uptake by certain plants of $Pb(NO_3)_2$ containing some Thorium B (Pb^{212}). After given intervals of exposure, the plants were ashed and the radioactivity determined. Later similar work with this technique, using active K, Ca and Na, by Overstreet *et. al.*, and Stout *et al.*, showed that in general cation uptake by plants was determined not solely by simple physical permeability but also by internal metabolic factors.

In some cases it might be desired to determine whether a given intermediate occurs. Such a problem is illustrated by the study of Medes, Weinhouse and Floyd[2] who made a study of the kidney oxidation of fatty acid. In mammalian liver fatty acids are known to be converted to acetoacetic acid. In the kidney however this was not known to occur despite the fact that acetate, which is formed, is generally thought to go to acetoacetate during oxidation. Two alternative explanations were possible, (1) that kidney oxidation does not take the same metabolic path as in liver or (2) that acetoacetate is formed but is oxidized too rapidly to be detected by ordinary means. In order to determine which of the explanations was probable, a mixture of labelled acetate containing C^{13} and normal acetoacetate was incubated with kidney slices for a time sufficient to oxidize some, but not all, of the acetoacetate. At the end of the experiment acetoacetate was isolated in pure form and it was found that this acetoacetate contained some of the C^{13}. This result is obviously consistent only with the latter alternative.

Analytical Techniques: Isotope Dilution

Although quantitative methods exist for the estimation of most biological compounds, analysis of mixtures is most often difficult or impossible and subject to a varied degree of accuracy due to interfering substances. A method, using labelled compounds was developed by Rittenberg and Foster[3] which eliminated the errors of analysis and became a particular method of greatest accuracy and specificity. The operation of this technique is best illustrated by an example. In determining the amino acid composition of a protein hydrolysate, numerous difficulties present themselves. There are about twenty different amino acids which must be separated quantitatively and estimated by specific reagents which are usually not available. In using the isotope dilution technique the procedure is to synthetize the specific amino acid so as to contain a labelled atom *e.g.* N^{15}, C^{14}, S^{35}, H^2. An accurately weighed amount of this labelled compound (w) is added to the mixture which will dilute

it with the amount of the unlabelled amino acid originally present (W). To detect the amount of dilution w/W+w, it is only necessary to isolate *any* amount of very pure amino acid. It can then be shown that w/W+w=specific activity after mixing/specific activity before mixing, from which W is easily calculated. This method is highly specific and is limited only by the purification procedures and the sensitivity and accuracy of the methods of estimating the isotopes. In the case of amino acids the accuracy thus far is considered about 1%.

A modification of this technique was developed by Keston *et al.*[4], which may be called an inverse dilution method. The method consists of treating a small amount of protein hydrolysate with "Pipsyl Chloride" (para iodophenyl sulfonyl chloride) so as to obtain a complete reaction. The iodine in this compound is the radioactive isotope. To this mixture of sulfonamides is added an accurately weighed and relatively large amount of the unlabelled sulfonamide of the amino-acid. The isolation procedure and calculations are similar to those described under isotope dilution. This procedure has the advantage that it is not necessary to prepare all of the labelled amino acids and reduces preparations only to that of pipsyl chloride.

Physiological Applications

A. Permeability Studies: The tracer method affords an almost perfect means of studying cellular permeability since it becomes possible to study diffusion processes in cases where no net transfer occurs. It has often been stated that Na* is not diffusible through erythrocyte membranes. Cohen and Cohen[5] injected $Na^{24}Cl$ intravenously into dogs and at intervals withdrew blood samples. These were centrifuged and the serums separated. The cells were washed. The serum and cells were then analyzed for Na^{24} content. It was found that the ratio of the activity in the cells to the activity in the plasma rose in a few minutes to nearly 80% of the value which would be expected for complete equilibration. For the in-vitro studies they took washed cells and equilibrated them against aqueous solutions of $Na^{24}Cl$ and determined the rate of uptake of Na^{24}. From these experiments they were able to conclude that Na does readily diffuse in and out of cells both in-vivo and in-vitro. In a similar manner Hevesy and Hahn showed that in rabbit erythrocytes 25% of the cellular potassium is replaced by plasma potassium.

Metabolic Turnover

With the introduction of tracer techniques the rapid turnover of metabolites was readily demonstrated. Schonheimer and Stetten fed palmitic acids labelled with Deuterium to rats. After 8 days the rat lipids was analyzed and found to contain 44% of the Deuterium of which 24% was present in the palmitic acid and the remainder in varying amounts in stearic, myristic, lauric, palmitoleic and oleic acids. The interconvertibility was demonstrated similarly with labelled oleic acid. This interconversion was found in both fasting animals and those on fat adequate diets. It was also found that linoleic acid and other essential fatty acids do not seem to enter these interconversions. From this type of experimental finding Schonheimer was led to the working theory that in living organisms there is a continual synthesis and resynthesis of metabolities in which metabolic components, viz. fatty acids, amino acids, nucleic acids, sugars, etc. are involved in rapid chemical reactions. Linkages are opened, liberating molecular fragments or atomic groupings which merge with other fragments derived from all the macromoles and ingested materials to form a "metabolic pool" with components of indeterminate origin. Counteracting this degradation is a resynthesis, deriving fragments from this metabolic pool and restoring body components. The ever increasing body of data that has been accumulating has tended to confirm this conclusion in respect to such a diverse group of metabolic processes as the metabolism of fats, metabolism of proteins, the metabolism of nucleic acids, etc.

In regulation mechanism studies tracer methods also play an important role. These mechanisms must be established both in-vivo and in-vitro, especially the former. In this case it is possible to trace the exchange of materials between vari-

ous parts of a cell or organism. As an example consider the phosphorylative mechanisms in metabolizing yeast cells. Under anaerobic conditions glucose is fermented by a series of oxidation steps, forming a complete cycle which has been elucidated by the researches of Meyerhof, Parnas, Warburg, Cori and others. Essentially the scheme involved the formation of phosphate esters of carbohydrates and metabolic products. If yeast cells are incubated with glucose in the presence of P^{32}, about 40% of the extra-cellular phosphorous is exchanged in a few hours. In the absence of nutrient no P^{32} is taken up. This finding has been confirmed by a number of independent workers. The absence of phosphate exchange under this specific condition may be due (1) to the fact that there is little exchangeable phosphorous in yeast or (2) that the yeast cell is impermeable to phosphorus. In view of the earlier discussion on permeability the latter alternative seems improbable. To confirm the first alternative Kamen carried out the incubation in the presence of sodium azide. In passing it should be mentioned that sodium azide will permit the fermentation of glucose by yeast cells to give alcohol and CO_2 but will prevent the assimilation of glucose into yeast cell structure. Under these conditions the uptake of P^{32} was reduced to 2% of that in the absence of azide. This proved that the cell can absorb the phosphate but that little directly exchangable phosphate exists in the cell.

Locational Problems

Among the most obvious isotope uses are those involving the determination of the site of deposition of a labelled material. When radioisotopes, having strong radiations, e.g. I^{131}, are ingested, the general location of the concentration can be determined by a simple scanning with a GM tube. In the case of radio-active isotopes with weak radiation small GM tubes may be used — inserted in a blood vessel, as was used by Hamilton[6] for studies of the uptake of ingested Na, K, Cl, Br, and I. In a similar manner the rate of blood circulation has been studied and sites of impaired circulation indicated[7].

In the use of stable isotopes it is evident that locational problems involve sacrifice of an animal and analysis of the tissues. In this manner[8] it has been indicated that proteoses and peptones seem to concentrate principally in the skin.

Another type of locational technique is the production of radioaudiographs. In this technique, as with x-ray photographs positioning can be estimated. Of a more biological interest is the use of sectioned tissue and the determination thereby of the localization within the cell of chemical substances without destroying the section. A. Claude (Biol. Symposia Vol. 10, 111, 1943) developed a technique at the Rockefeller Institute for gently breaking cell walls of tissue and by differential centrifugation to separate the separate formed constituents in bulk (nuclei, secretory granules, chromatin, chloroplasts, etc.). These cell elements were then available for estimation of radio and stable isotope concentration.

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LESSONS FROM OPERATION CROSSROADS

COMMANDER C. A. ERICKSON, C.E.C., U. S. NAVY

The lessons from Operation Crossroads are of vital concern to all of us. Naturally, the lessons are of utmost importance to military men in connection with security of the country. This makes them important to all. Aside from the military aspect, the lessons of Crossroads for peace time uses, such as medical research, radiological safety, and the study of plant life will prove to be of great benefit.

Although I did not witness the atomic bomb tests at Operation Crossroads, I have completed two courses of instruction given by the Navy in atomic matters and have visited and measured radiation on three of the target ships from that operation. At present I am pursuing a course in Atomic Energy Engineering at the Naval Postgraduate School.

The decision to make the atomic tests at Bikini came as a result of the evaluation of the damage at Hiroshima and Nagasaki. The Joint Chiefs of Staff, with the approval of the President, decided that a scientific test of the capabilities of the bomb was necessary. It was considered necessary to determine the effect of the bomb on ships, military ground equipment, and airplanes.

The tests would afford practice in scientific procedure, and practice in use of theoretical safety measures. By the use of animals and control procedures it would provide medical data for further study of radiation sickness. The Air Force which delivered the bombs to Nagasaki and Hiroshima would be afforded additional experience in the use and handling of the bomb. The main mission however was to learn about the damage which could be done to naval ships.

Three tests were scheduled, test Able with the explosion in the air; test Baker, with an underwater explosion, and test Charlie, a deep underwater explosion. Tests Able and Baker were accomplished at Bikini. The third test was postponed by the Joint Chiefs of Staff and not accomplished at Bikini.

All services and branches took part in the tests, operationally and for procurement of special data. In addition there was a Civilian Evaluation Commission functioning under the President with Senator Hatch as Chairman and an Evaluation Board under the Joint Chiefs of Staff with Dr. Karl Compton as chairman.

The bomb for the first test was dropped by the Army Air Force B-29 on July 1, 1946. The cloud from the air burst rose to a height of about 40,000 feet forming mushrooms on the way up. The report of the Evaluation Board has the following to say concerning this test:

"a. The bomb exploded with an intensity which approached the best of the three previous atomic bombs, over a point 1500 to 2000 feet westerly of the assigned target, and at approximately the planned altitude. The target array in no sense represented an actual naval disposition, but was designed to obtain the maximum data from a single explosion.

"b. A destroyer and two transports sank promptly, and another destroyer capsized. It later sank, and the Japanese cruiser Sakawa sank the following day. The superstructure of the submarine Skate was so badly damaged as to make it unsafe to submerge the vessel. The light carrier Independence was badly wrecked by the explosion, gutted by fire and further damaged by internal explosions of low order, including those of torpedoes. All the above vessels were within one-half mile of the explosion point.

"c. Numerous fires were started on other ships. Here it should be remembered that the target ship decks carried a great variety of test material not ordinarily exposed on the decks of naval vessels.

"d. The only major combatant ships within one-half mile of the explosion were the battleships Nevada and Arkansas and the heavy cruiser Pensacola. Apparently little damage was done to their hulls or their main turrets, but their superstructures were badly wrecked. These ships were unquestionably put out of action and, along with many others

within three quarters of a mile, would have required extensive repairs at a principal naval base.

"e. Other ships in the target array suffered damage in varying degree, depending on position and type of ship, but there was relatively little damage at distances greater than three quarters of a mile.

"f. Examination of the flash burn effects produced by the initial radiation from the explosion indicates that casualties would have been high among exposed personnel. However, it is the opinion of the Board that persons sheltered within the hull of a ship or even on deck in the shadow of radiation from the bomb would not have been immediately incapacitated by burns alone.

"g. Within the area of extensive blast damage to ship superstructures there is evidence that personnel within the ships would have been exposed to a lethal dosage of radiological effects."

The bomb for the second test, Baker, the underwater test, was brought to the target area by a small ship. The bomb was exploded by radio signals from a ship outside of the lagoon. The underwater explosion made an impressive sight as the fire ball came through the surface of the water. However the upper air appearance of this explosion was not as impressive as the air explosion. The cloud rose to a height of 5,000 feet.

The Board has the following to report about test Baker:

a. The explosion produced intense radioactivity in the waters of the lagoon. Immediately after the burst, it is estimated to have been the equivalent of many hundred tons of radium. A few minutes exposure to this intense radiation at its peak would, within a brief interval, have incapacitated human beings and have resulted in their deaths within days or weeks.

"b. Great quantities of radioactive water descended upon the ships from the column thrown over them by waves. This highly lethal radioactive water constituted such a hazard that after four days it was still unsafe for inspection parties, operating within a well established safety margin, to spend any useful length of time at the center of the target area or to board ships anchored there.

"c. As in Test Able, the array of target ships for Test Baker did not represent a normal anchorage, but was designed instead to obtain the maximum data from a single explosion. Of the 84 ships and small craft in the array, 40 were anchored within one mile and 20 within about a half-mile. Two major ships were sunk, the battleship Arkansas immediately and the heavy hulled aircraft carrier Saratoga after seven and one-half hours. A landing ship, a landing craft and a concrete oil barge also sank immediately. The destroyer Hughes in sinking condition and the transport Fallon, badly listing, were later beached. The submerged submarine Apogon was sent to the bottom, emitting air bubbles and fuel oil, and three other submerged submarines sank; but two of these were later raised. The badly damaged Japanese battleship Nagato sank after 4½ days. It was found impossible immediately to assess damage to hulls, power plants and machinery of the target ships because of radioactive contamination. External observation from a safe distance would indicate that a few additional ships near the target center may have suffered some hull damage. There was no *obvious* damage to ships more than half a mile from the burst."

The President's all-civilian Commission, whose chairman was Senator Hatch of New Mexico, substantially agreed with the reports of the Board.

The tests showed the Navy several things:

a. Ships at anchor and ships in tactical formation must be widely spaced.

b. Design changes on ships should be effected to reduce damage above water and to provide greater protection to the crew.

c. They provided data by which the Navy could intelligently cope with this new weapon, offensively and defensively.

d. The adequacy of the theoretical safety measures was proven.

In addition the tests provided quantitative data on what to expect from an atomic burst.

Phenomena Accompanying an Atomic Burst

The main phenomena accompanying an atomic burst are pressure waves, rays from unfissioned material, rays from products of fission, penetrating rays, and non-penetrating rays.

The shock wave, one of the pressure waves, is generated by the very rapid expansion of gases. It has an initial velocity of about 25,000 ft. per second. The velocity soon drops to 9,000 ft. per second which is the velocity of a shock wave from a dynamite explosion. These velocities are much higher than the speed of sound. The wave compresses the gases in front of it thereby building up pressures in the air. After the shock wave has passed, a rarification of the atmosphere and marked decrease in pressure occurs. Thus, the pressure will go up immediately in front of the shock wave and, a short time later, the pressure will drop. The effect is to push an object rapidly one way and then the other like two enormous hammer blows from opposite sides, and at the same time to compress the object and then explode it.

The mach wave, another pressure wave, is caused by the interference of a shock wave reflected from the ground combining with the original shock wave. The mach wave is peculiar in that the pressure effect is larger than the sum of the two effects from the interfering waves producing the manifestation.

It is known that an atomic burst is nowhere near 100 per cent efficient and that after a burst there is a high percentage of unfissioned bomb material left. This material is made incandescent and then vaporized by the bomb burst; later it condenses and falls to the ground as a very fine material. This material emits alpha rays. The alpha particle is a nucleus of the helium atom and streams of these particles are alpha rays. This ray is stopped very quickly by skin, paper, or any other similar material and therefore is not dangerous while outside of the skin. Danger lies in alpha-emitting material getting inside the body where, for a long period, it will continue to emit the alpha rays. Alpha rays inside the body are particularly destructive, since they cause a very heavy ionization which in turn affects the tissues. The safe dose during the lifetime of any one person for alpha-emitting material is one-millionth of a gram. This small quantity will, during the lifetime of a person, emit enough alpha rays to cause such extensive ionization and changes in the tissues as to be extremely dangerous. In general, then, the alpha rays themselves, when received from outside of the body, are not dangerous, but a small quantity of alpha-emitting material inside of the body is very dangerous.

Fission products are the new elements formed after a bomb burst. These elements are generally in the middle range of the periodic scale. They are generally not stable and emit neutrons, beta rays and gamma rays in an attempt to become stable. Beta and gamma rays are both penetrating rays. Protection consists of being sure that the dosage limits for these radiations for one day are not exceeded. Thus, a person could go into a heavily contaminated area, provided he stayed there only long enough to get not more than the daily safe dose. In certain radiological areas, a man may work in a contaminated locality for only six minutes, smaller periods not generally being practicable. As the activity decreases, or is shielded by lead or other materials, the safe working period is increased accordingly.

Non-penetrating emissions are infra-red rays which are manifested as heat, visible rays and ultraviolet rays. Protection against these rays is afforded by white clothing. During the two bombings in Japan, many people at certain critical distances from the bomb, where other effects were not important, were saved from extensive injuries by simply having clothing on their backs.

It should be kept in mind that while the atomic bomb introduces hazards of a radiological nature which are new and different from the hazards of older bombs, the usual hazards of blast, and fire are also present. In fact these old hazards are more dangerous than those from the rays. It is estimated that atomic bomb injuries are divided as follows: from blast effect—50%, from burns—20%, and from

radiological hazards—30%. Some estimate the percent injuries due to radiological hazards even below 30%.

Zones of Damage for an Atomic Burst

Operation Crossroads, together with the bursts at Nagasaki, Hiroshima, and Almogordo, provided data for estimating zones of damage.

Using a bomb of about 40,000 ton high explosive potency exploded about 3,000 feet in the air, certain zones of damage to the surrounding area have been established. These zones are based on level ground since hills have a decided shielding effect. Also distances and description of conditions in each zone are of necessity an averaging of past explosions and a projection of the data. The descriptions are essentially educated guesses.

The area within a one-half mile radius of the ground zero is a doomed area. A condition approaching total destruction would occur. The only conventional structures that would even partially survive the blast would be heavy steel and reinforced concrete type of structures, and they would have to have very thick reinforced roofs and floors, heavier than the usual warehouse type construction. Brick buildings would be crumpled to piles of rubble. Steel frameworks would be twisted and broken from the heat and from the intense pressures both inward and outward, forward and backward. Reinforced concrete floors, particularly on the lower floors and on the ground level, would remain in place if not too close to the burst. The general effect throughout the entire area would be one of total destruction. It would resemble one huge pile of debris. Frame buildings, of course, would be immediately smashed and then subjected to general fires from the burst, from electrical short circuits, or from other secondary causes. Total destruction would not be limited to the first half mile, however. There would be equivalent total destruction out to the one mile radius.

The effects upon personnel within a one mile radius will be as bad as the structural damage. That is—almost total destruction. Within this area there will be so many lethal influences—heat, shock, radiation, intense light—that there will be practically no chance for survival. Those shielded from the direct heat rays but exposed to the gamma rays will receive lethal doses of radiation exposure. If shielded from heat and radio activity, they will be subjected to a terrific rain of falling missiles. There will also be fire and suffocation by exhaustion of the oxygen supply. Exit from the area will be almost impossible due to the great piles of debris. For practical purposes, then, a zone within a one-mile radius must be considered doomed and abandoned.

From one to two miles away from the burst, heavy damage will occur, but generally the area will be worthy of some post-explosion activity for the purpose of saving life, salvaging property, and stopping fires. The damage will be considerable. All wood frame buildings will be completely destroyed. Wall-bearing masonry buildings will receive heavy structural damage. There will be considerable damage from flying debris and secondary fires. Heavy reinforced-concrete buildings will receive moderate structural damage. Water mains underground would generally remain intact. Underground power lines would be intact, but overhead lines would be destroyed. Railroads would be heavily damaged but susceptible to reconditioning, if necessary. A heavy railroad bridge would probably withstand the explosion in this area. Damage to roads and streets would be negligible but there would be considerable blockage of streets from debris. Heavy fire damage would occur, from secondary causes. Generally, it would be practicable to fight fires with the best means available. Damage to personnel will depend on their location with reference to the burst and any shielding afforded by intervening structures. Those exposed to the direct rays will receive severe burns and in some cases the penetrating radiation will cause fatalities. Fatality may not occur until after radiation sickness has caused a severe illness.

From two to three miles from the burst a zone of moderate damage can be anticipated. The heavy damage in this area will probably be confined to wood frame buildings of very light construction. Brick, concrete and steel buildings will stand the blast fairly well and will afford

protection to lower buildings by shielding. In this zone the horizontal angle of the direction of the blast becomes very flat. There is still a great danger from fire in this area. Personnel exposed to the direct rays will be slightly burned. Radiological dangers due to the primary blast will not be great. The greater hazards in this zone are from flying glass, falling plaster and missiles. Since personnel in this zone will not be seriously injured and will have their wits about them to some extent, they will not be subject to panic and mass hysteria. Personnel in this zone, if properly trained, should be able to help themselves a great deal, receiving outside aid as possible and furnishing some aid to personnel in more heavily damaged zones.

Outward from the three mile radius to the four mile radius the damage will be comparatively slight in comparison to damage in inner zones.

If the terrain is hilly or mountainous, a ridge would prevent serious effects from extending beyond it.

There is one other very important danger point and this is the fall-out zone caused by radioactive materials being carried aloft by the draft of the explosion and then carried in the direction of the wind as they are settling. Depending on the direction of the winds aloft, up to the 50,000 ft. elevation these particles would be carried varying distances. They would cause a heavy concentration when the particles finally reached the ground, say 15 to 20 miles from the burst, in that the particles are radioactive and emit dangerous quantities of radiation.

The lessons of Crossroads are not complete. A continual study of the ships, materials and animals is being made, and our knowledge will be increased as the studies are completed.

It is sincerely hoped that these remarks will increase your interest in atomic energy and that you will pursue a further study of this new subject.

PATHOPHYSIOLOGICAL EFFECTS OF TOTAL BODY IRRADIATION

ELIZABETH E. PAINTER, Ph.D.*

Little has been written or discussed publicly about the potential hazards, immediate or delayed, of introducing radioactive materials into the patient, or of handling these materials preparatory to their administration. It is essential that clinical men be aware of the hazards involved for themselves, for the patient receiving diagnostic dosages and for the patient receiving therapeutic dosages. Indeed, an adequate knowledge of the half-life or decay of the isotope, of its distribution in the body, of the rate of its excretion and of the age and life expectancy of the patient (and of the physician) is of prime importance for the intelligent handling and administration of radioactive materials. Finally, after the material has been given, the clinical course should be carefully followed with frequent checks on the blood picture to detect and to evaluate the effects of the radiation. Once the isotope has been introduced into the body, there is no method yet available for reversing the radiation reaction. *There is no antidote for overdosage.* For this reason, it is appropriate to discuss the pathophysiological effects of total body radiation in some indefinite sequence, pointing out those disturbances which occur at relatively low dosage exposures as well as those occurring at higher energy levels.

When the animal body is subjected to ionizing radiation the clouds of ions formed in and around tissue cells initiate a long chain of events which may ultimately lead to death. The picture which develops and the conditions resulting in death differ according to the rate at which the dose of radiation was given and the time that the animal or man lives after the initial exposure. Some of the physiological and biochemical alterations appear to result from direct damage to the tissue concerned, while others result from indirect effects by agents carried in the blood from one region of the body to another. Research needs to be directed toward separating the direct from the indirect effects of radiation and toward identifying the toxic agents.

The signs and symptoms are similar with every kind of ionizing radiation whether it be penetrating external radiation, namely, X-ray, gamma ray, or neutrons or internal radiation from deposited radioactive material, either alpha, beta, or gamma emitters. The physiological signs of damage are nonspecific, and nearly every organ system in the body may be affected.

One evidence for differences in the mechanism of killing is that deaths occur in waves after a single dose, and with different dose rates of daily exposures discontinuities occur in survival times. In practice, dose rates may range from the radiation flash of an atomic bomb detonation to the dose accumulated over many years from a small deposit of radioactive material in the body.

In order to obtain some definite pattern in the pathophysiological state, controlled experiments on animals have been performed and have been found to agree extremely well with some of the findings after the Japanese bombings and the Bikini tests. Controlled experiments on a quantitative scale using X-ray were necessary to exclude the complications produced by thermal or mechanical disturbances as occurred in the bombings and other tests. Actually, when irradiation is given as a single total-body dosage of X-rays, the quantity necessary to kill 50 per cent of the animals in 30 days or less is relatively small:

175-200 r for the guinea pig
325 r for the dog
350 r for the goat
400-500 r for man(?)
530 r for the mouse
600 r for the rat
800 r for the rabbit
2000-3000 r for the frog

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The characteristic phases in the pattern which occurs after an LD 50 dosage can be divided into: the initial shock phase or radiation sickness, beginning after a latent period of one hour following the radiation and lasting sometimes as long as twenty-four hours; acute phase lasting from nine to twenty-one days; subacute phase lasting from thirty to two hundred days; and the chronic phase, from two hundred days on. Manifestations differ somewhat in the various species, but the same general pattern is seen in all.

Initial Shock. After an LD 50 of external radiation, there occurs a latent period of one to two hours in the different species, during which time no significant physiologic changes are observed. The dog, rat, mouse, guinea pig, goat and man show signs of radiation sickness during the first six hours. This condition is characterized by prostration, diarrhea, urination, lacrimation and decreased food and water consumption. Some rabbits as well as chickens will die at three to forty-eight hours. In addition, rabbits show granulocytosis during the first twenty-four hours and a marked fall in blood pressure, approximately 50 to 60 per cent below the control levels one to two hours after irradiation. The change in pressure is due in part to autonomic factors as shown by partial protection with atropine or by vagotomy and in part to circulating factors as shown by transfusion experiments. Control studies on normal recipients from which half the blood volume had been removed and gradually replaced with the same quantity of blood from normal donors showed a 5 mm. change in blood pressure, whereas normal recipients transfused in a similar manner with blood from irradiated donors showed a 26.5 mm. drop in pressure. These circulatory changes are accompanied by leakage of plasma and its constituents from cutaneous vessels, observed as more rapid diffusion of the blue dye, T-1824, and of fluorescein in the locally irradiated than in the normal skin.

In man and in the dog, nausea, vomiting and anorexia occur during this early period, but there appears to be no significant change in blood pressure. For the most part, changes in blood and tissue chemistry in all species examined are slight.

Acute Period. This is the period when most of the animals given a thirty-day LD 50 of external radiation die. Generally, animals show recovery from the initial lethargic state a few hours after irradiation and remain in apparently good clinical condition until the seventh or eighth day. The depression that follows may be either gradual or abrupt and may occur at any time in the next few days. Before clinically visible changes appear, however, there are alterations in many physiologic systems. The most sensitive systems, i.e., those showing the earliest changes with the lowest dosages of radiation,* are the blood forming organs, the gastrointestinal tract and the gonads. The absolute lymphocyte count declines abruptly, whereas the count of granulocytes declines more gradually (after the initial granulocytosis in rabbits). Diminution in number of circulating lymphocytes is the most sensitive evidence of exposure yet found. Evidence of the changes in other systems is manifested on the third or fourth day by increased sedimentation rate of the blood cells and prolonged clotting time. On the sixth to the tenth day, there is an increased plasma clearance of phenol red (with return to normal about the twelfth to the fourteenth day), an increase in the plasma volume as the red-cell volume decreases, rise in blood sugar, later followed by a fall, increase in plasma histamine, hep-

* Effects of Threshold Dosage of Total Body X-rays

Dosage	*Effect*
25 roentgens	Lymphopenia (dogs, rabbits, rats)
50 roentgens	Granulocytopenia (dogs)
	Reduction in platelet count (dogs)
	Reduction in blood pressure (rabbit)
	Elevation of basal metabolism (rats)
	Inhibition of intestinal absorption of glucose (rats)
100 roentgens	Granulocytopenia (rabbits)
	Elevation of sedimentation rate (dogs)
	Anemia (dogs, rabbits)
200 roentgens	Absence of reticulocytes (dogs)
	Prolongation of clotting time (dogs)

arin, cholesterol and acetone bodies, diminution of plasma non-protein nitrogen, urea nitrogen, "polypeptide nitrogen" and total proteins followed by a late increase, decrease in fecal and urinary coproporphyrin, elevated urobilinogen and bilirubin, lowering of gastric acidity, reduced absorption of glucose by the intestine and delayed emptying of the intestine, and ulcers begin to appear in the mouths of dogs. The relation of these numerous findings to the underlying physiologic and structural changes and to compensatory processes is not in all cases clear.

The late (or terminal) changes occur precipitously three or four days before death, and some of them may appear briefly in survivors before a gradual recovery sets in. These include scattered petechiae and diffuse hemorrhages in the skin, a marked rise in heart rate, a gradual fall in blood pressure, and increase in body temperature and, in some animals, edema of the neck and mediastinal regions. The cardiovascular damage has been observed most frequently in the dog. Changes in the heart are indicated by the change in the electrocardiogram, which shows a slight increase in the P-R interval, a low take-off and an inverted T-wave in Leads I and II. This has been most obvious in animals that, on autopsy, showed extensive hemorrhages in the cardiac muscle. Changes in the peripheral circulation are apparent in many ways; there is difficulty in drawing blood from small vessels; clumping of red cells with loss of plasma from vessels can be seen microscopically: and slight trauma to skin results in ecchymosis or edema. On autopsy, widespread hemorrhage and petechiae are found throughout all the tissues, including the central nervous system and the kidneys.

A highly significant factor in the bleeding tendency has been described by Allen and Jacobson who observed that a greatly increased heparin concentration ran parallel to the prolonged clotting time. The progressive hemorrhages were stopped and the clotting time was returned to normal by the administration of toluidine blue or protamine, both of which inactivate the heparin.

In this later period there is also evidence of liver dysfunction as shown by the changes in bile-pigment metabolism. Plasma non-protein nitrogen and urea nitrogen show a marked rise, associated with the increase in body temperature, with the decreased kidney function and with an increase in total tissue breakdown. The latter has been determined by direct and indirect metabolic measurements. At this stage the picture is typical of a general toxemic reaction. Toxins may be expected in the presence of bacterial infections occurring with the extreme leukopenia and may also come from the products of tissue breakdown or of extravasated blood.

Subacute Period. Animals surviving a single LD 50 of radiation for thirty days or longer fall into this category. Dogs receiving daily X-ray dosages of 25 r or below or low dosages of the internal emitters, plutonium or strontium[89] (radium in man) will die between thirty and two hundred days.

The characteristic changes during this period are severe anemia, emaciation, loss of hair and pigmentation of the skin; terminally, ulcers are found in the duodenum and jejunum of dogs. The animals that receive the internal emitters of daily dosages of X-rays do not show the early shock-like symptoms, but they may show from two to four depression waves between the original injection, or the first expose to radiation, and death. These are manifested by reduction in the red-cell count, by general lethargy and by decreased food and water intake. Hematologic changes develop very gradually and show fluctuations with the depression waves, as do the changes in other physiologic systems. Several days prior to death there occurs an increase in heart rate and an increase in body temperature similar to the changes observed in dogs in the terminal phase of the acute period.

Chronic Period. In animals receiving still lower dosages of X, alpha or gamma rays decreased life-span, graying of dark-haired animals and the development of tumors constitute the chronic changes after irradiation. In mice, lymphomas, lymphatic leukemia, and lung tumors are readily induced by total body irradiation. Many species develop tumors of certain

tissues after local irradiation by alpha-emitting or beta-emitting substances. Especially noteworthy are the multiple skin tumors resulting from external beta irradiation and bone tumors following absorption of radium, strontium^{89}, plutonium, and other radioactive isotopes. In addition to high incidences of malignant tumors in areas receiving relatively heavy dosages of radiation, the normal tumor incidence in various species of animals is increased (or tumor development is accelerated) after either a single high dose or repeated or continuous exposure at a low level.

No single clinical reaction is peculiarly specific for radiation damage. A similar preterminal course with leukopenia and high sensitivity of dividing cells is found with such agents as the nitrogen mustards and urethane; the acute terminal course with fever and petechiae is characteristic of acute infections and of many diseases. There are striking similarities to anaphylactic shock and to the nonspecific alarm reactions to a variety of diverse toxic agents given in sublethal amounts, and to the granulocytic states accompanying drug sensitization. Many of the delayed effects of radiation can be duplicated by various toxic chemicals, such as anemia and leukemia in benzol poisoning, or tumor induction by hydrocarbons or ultraviolet light.

Many of the features of the radiation damage can be accounted for by destruction of the sensitive cell types. There is some evidence that loss of granulocytes, rather than loss of lymphocytes, correlates with the lethal dose among the various species of animals. Many of the early changes such as increased renal blood flow and the elevated sedimentation rate, suggest the presence of circulating toxins, whereas many of the late changes appear to be associated with hemorrhage due to the release of heparinoid material into the blood, probably from injured cells.

MEDICAL USES OF RADIOACTIVE ISOTOPES

LEONIDAS MARINELLI, M.A.*

The subject, "Medical Uses of Radioactive Isotopes" would have been a very interesting, but brief, topic about eight years ago. This field, however, has widened and increased to such an extent that there would be difficulty in including it in a book. Therefore, you will appreciate the fact that my presentation cannot be complete and that all I can do is to give you a glimpse of the field. The glimpse will be through the eyes of a physicist. I hope, nevertheless, it will suffice to illustrate the importance of radioisotopes in medicine, both as a tool of research and as a tool of therapy.

The use of certain isotopes is based upon our ability to distinguish them from the natural isotopes which exist in the body. They need not be radioactive. For instance, if one uses ordinary iron one has isotopes of mass — 54, 56, 57, and 58, with abundance of 5.81%, 91.64%, 2.21%, and 0.34%, respectively. It is obvious that if one enriches by means of special separation the isotope Fe-58, of the iron introduced into a patient, the iron thus used will be somewhat different from the natural one. One, then, could trace with a mass-spectrometer, iron containing 10% of Fe-58 down to the natural level. If one can measure the Fe-58 background to 0.01%, it is obvious that Fe-58 can be traced down to a dilution of 1000.

Human curiosity, however, is unbounded, and in many problems this stable isotope would be practically useless. Dilutions of the order of 10^5 and above can be tracked down with radioactive isotopes because they are not found in nature.

Fe-55, with a half-life of four years, or Fe-59, with a half-life of about 47 days, can be put into the system one is studying, and traced to levels which depend solely upon the sensitivity of the detecting apparatus and the radioactivity of the background.

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The advantages of radioactive isotopes over stable ones are several: they are cheaper and easier to measure; they require less chemical manipulation as far as measurements are concerned; they can be traced to greater dilution and they are much more versatile. However, they do emit ionizing radiations and, therefore, cannot be used indiscriminately and in unlimited quantities. As a matter of fact, the quantities which we can use in tracer work are rather small and may tax, sometimes, our ingenuity in detecting them.

Of the two fields; namely, medical research and therapy, the first is the one which probably will benefit most by the use of radioactive isotopes.

A few of the fields in which these isotopes are particularly suitable are: intermediary metabolism, permeability and membrane transfer, utilization by specific organs (including histological or cytological entities), tagging of complex compounds, and measurement of the so-called fluid spaces.

I have said that radioactive isotopes were versatile; this property derives from the fact that their radiations can be detected in a variety of apparatus and under many conditions.

One can, for example, study the concentration of radioactive iodine in blood following the oral administration of NaI for a period of over thirty-five days. When this was done, we were able to follow in about 0.1% of the blood volume, 1.5% of the dose through more than four half-lives; namely, we could measure fairly accurately one-millionth of the original amount.

Another example is the localization of a radioactive isotope in histological specimens by means of radioautographs.

A radioactive isotope can be studied and located *in vivo* under favorable circumstances. One can, for example, measure the radioatctivity in the neck ef a patient given radioactive iodine. In one experiment the patient was given I^{131} and

the radioactivity over his neck diminished on account of nuclear decay and thyroid turnover of the radio element. On the seventh day, the first of 4 daily doses of thyrotropic hormones was given. On the eleventh day a sharp drop in radioactivity occurred. On that day we gave a tracer dose of 144 microcuries. Of this, 90% was taken up by the thyroid and only 9.3% excreted; whereas, the initial dose (200 microcuries) was excreted to the extent of 40% and taken up by the thyroid to the extent of 30%. We concluded that the thyroid, after the administration of thyrotropic hormone, had mobilized the I^{131}. We followed this and on the thirteenth day gave 488 microcuries of radioiodine. The radioactivity measurement disclosed a retention of 47%, and the excretion was 14.4% as though the effect of the thyrotropic hormone was wearing off as time elapsed. As a matter of fact, we repeated the test on the 21st day and found that the uptake was only 7% and the excretion 69%. Here you have, in a single experiment, on a single patient, quite a detailed picture of the effect of thyrotropic hormone administration on the I^{131} uptake of a thyroid; namely, a flare-up in avidity which, however, decreases steadily and terminates in a refractory state. Whether or not this was due to the release of thyroglobulin in the blood or not is beside the point, but the fact remains that it does take place.

An isotope of sodium has found extensive use in medicine. Sodium 24 is a short-lived isotope which emits both beta and gamma radiations and can be thus detected outside of the body. It has been used in studies of hypertension.

A standardized dose of sodium chloride was administered by venous injection in one arm, and the time which elapsed between the injection and the reading over the foot was plotted as abscissa and the readings themselves were plotted as ordinates. In normal patients two limiting curves were obtained. In one particular case of hypertension, the sodium took quite a long time to reach the foot. However, after a thoracolumbar sympathectomy, the patient fell within or slightly above the normal time. One of the conclusions obtained by the authors, Dr. Smith and Dr. Quimby, was that not all patients with hypertension would respond to sympathectomy; and they think that the study which Na^{24} affords will permit the physician to select a case for sympathectomy. Sodium 24 has also been used as a guide to the efficacy of drugs used in the treatment of diseases of the peripheral vascular system. The work of Mufson, Quimby and Smith concludes that the patient with scleroderma, thromboangiitis obliterans, obliterative arteriosclerotic endarteritis, or non-specific arteritis of the minute vessels often show a subnormal curve for the diffusion of radioactive sodium from the blood vessels. They found also that histamine administered by ionophoresis or by infra-arterial injection brought about a definite rise in the diffusion curve. When given intravenously in one patient, it produced the opposite effect. The dilation caused by histamine was not reversed by 1 part in 250,000 of adrenalin given intravenously, and neither papaverine nor 5% NaCl solution given intravenously produced changes in the radioactive sodium curve

Sodium has also been used in studies of the retention of aerosols within the respiratory tract of man. As a matter of fact, this study can be done in two ways: by studying radioactivity over the chest of the patient, as well as over one of the limbs, usually the foot. The use of aerosols containing radioactive sodium has also led to the study of pulmonary resuscitative procedures as they affect the circulation. Of great general importance has been the work of Burch, Threefoot and Reaser on the correlation between radioactive sodium in plasma and radioactive sodium in urine excretion in normal man and in patients suffering from congestive heart disease. It was found that the concentration of plasma in normal man of sodium will fall to one-half in 13.3 days; if the patient has chronic glomerular nephritis, it will fall to one-half in 56 days. Patients with congenital heart disease will go down to one-half in 41 days. Those that are improving fast go down to 20 days, etc. The time taken for half of the sodium to be excreted is

also a very good diagnostic index of this condition.

If we look for another popular radioelement, we find Phosphorus 32, which emits beta radiation only. It has been used by Lawrence since 1936 in the treatment of leukemias. The use of P^{32} in these diseases is based on the fact that there is some degree of selectivity of localization and, hence, of irradiation in the tissues of interest. However, the degree of selectivity is not great; and the isotope is limited, like all others available to day, to the category of palliative agents. It seems to be efficacious in lymphatic leukemia more than it is in myelogenous leukemia. In 1939, the treatment of polycythemia was begun with satisfactory results; and Lawrence, in his last review of 74 patients treated from 1939 to 1946, shows that, in this group, the life expectancy is not far from normal. The series is not conclusive statistically, but it certainly shows that quite a good deal of help can be given these patients.

Lawrence demonstrated that the P^{32} uptake in the lymphatic tissue of leukemic mice is greater in the control. The same thing, to a lesser degree, takes place in the spleen although, after 60 hours, the two are not as different as they were at 24 hours. Now, these differences, although interesting and biochemically important, are not sufficient from the standpoint of decisive therapy. My feeling is that in leukemia, one has to obtain a factor of 30 or so before one really starts to get somewhere.

Some studies on mycosis fungoides constitute an example of what can be done with a beta ray isotope by studying it *in vivo*. The G-M counter was located over the cancerous lesions and analogous regions of the body which had no lesions, and the beta activity was recorded. Doses were given on two days; a large one, followed by three small doses later. This study established early the fact that not much could be done in the therapy of the disease because the radioactivity of the lesion was only five times that of most normal tissues. One could not hope to control these lesions which need several thousand roentgens with a ratio of that sort because this would require a prohibitive whole-body radiation of over 500 roentgens. If the ratio could be increased, however, the therapeutic outlook for this isotope might be entirely different.

Another interesting study is that of Marshak, on the uptake of P^{32} in the nuclei of cells. The P^{32} content of nuclei of tumor cells in lymphomas as a function of time from the injection of the animal is greater than that of normal liver, but this is not specific because the same results were obtained with regenerating liver.

Of possible fundamental significance to radiotherapy, are the studies of Hevesy on the effect of radiation on the synthesis of nucleic acids. In a series of papers Hevesy and his collaborators have shown that the synthesis of nucleic acid is retarded by radiation; this reaction appears very soon—during treatment, in fact—and the rate of synthesis tends to recover soon afterwards. The time at which recovery is completed depends upon the total dose.

I hope that these investigations will point the way toward a method of rational radiation therapy.

We come now to a subject with which I am slightly more familiar. That is the therapeutic problems dealing with radioactive iodine. The isotope of iodine which is readily available nowadays is I^{131} which has an 8-day half-life and emits both beta and gamma rays. It was investigated very early by Hamilton who studied the rate of diffusion in the blood, and rate of appearance in the hand soon after injection or oral administration; and, by means of radioautographs, the histological distribution of the isotope in the thyroid. In the case of Graves' disease, he demonstrated that the large acini have no radioiodine in them; whereas, the smaller ones contain more. In a case of carcinoma of the thyroid there were a few normal appearing colloids collecting most of the iodine and with the carcinoma showing none. In 1942, Keston, Palmer, Ball and Frantz showed, not by radioautographs but by external measurements, that the metastasis of a patient suffering from carcinoma of the

thyroid took up radioiodine. This observation reopened the field which had been dormant on account of the evidence available at that time; namely, the lack of correlation between carcinoma and radioactive iodine deposition. Soon after the paper was published in SCIENCE, I had occasion to work with Dr. Seidlin and Dr. Lighter at Montefiore Hospital on a cancer patient who had no thyroid (having been thyroidectomized about 19 years before) but who had extensive metastatic involvement and was suffering from hyperthyroidism. By superimposing a microphotograph of a metastasis on a radioautograph of the same, one could see that the tumor is followed faithfully by the shadow of the radioactive iodine. The clinical studies of this patient showed that he responded for a while to Lugol's Solution. His weight increased, his BMR came down slightly, his cholesterol rose slightly. The blood iodine did not show very much and, of course, there was no interest in the blood count at that time. Afte a while, the patient ceased to respond to Lugol's Solution. Soon after, the study with radioactive iodine was started. He had seven lesions, five of which were known at the time. We found the two unknown ones by giving him radioactive iodine and then examining him thoroughly with a Geiger counter. After the first dose was given to him, he responded favorably, gaining weight and showing all the other clinical indices of improvement; he was then tested with thiouracil and the tumors responded to thiouracil as though they had been normal thyroids. The patient is still alive after six years. This, to my knowledge, is the best result achieved so far. It is due, undoubtedly, to the fact that this patient did collect radioactive iodine in the tumors to a very high degree. Some calculations on dosage show that the radiation dose to the tumor was 300 times the dose to the blood. It can be seen immediately that if 50 r were given to the blood of this patient he would receive 15,000 r in the tumor, which would be quite a lot.

Another case was treated at Memorial Hospital. The patient was preterminal on admission. We knew beforehand that he would pick up radioiodine as a result of investigations conducted during the war, at which time we could not get enough radioiodine to treat him. By the time he could be treated, he had a great number of lesions. The outstanding one was over the femur and measured about 20-25 cm in diameter. He had to be treated rapidly, and two doses were administered within a week. One was 60 mc and the other was 120 mc. Their effect on the tumors was noticeable within 10 days, the largest tumor shrinking to one-fourth of its former size. However, we experienced something with this patient which we had not encountered before; within a short time he exhibited a thyrotoxicosis which was almost fatal. A sample of his blood was sent to Dr. Salter, who found that, at the time of the test, it contained 26 gamma per cent of protein-bound iodine. The normal is about four. Thyrotoxicosis is certain at 13.

After some time, during which he regained strength, we started to test him to see if he was receptive to iodine. We obtained consistent results and started to treat him again with 34 mc, 51 mc, and 34 mc of I^{131}. The symptoms of thyrotoxicosis reappeared, however, and he was put through a long course of thiouracil. After two days rest he was given a large dose of 122 mc without any trouble whatsoever. It is obvious that in cases of widespread metastasis of this type, one must consider what is happening to the thyroglobulin stored in them. They should not be released into the blood at a very fast rate or very serious complications will ensue.

At the end of a year of therapy the patient had gained 50 lbs. or so. This patient died of the disease 3½ years later. I feel that we might have saved him had we been able to treat him a little earlier.

While studying the reaction of thyroid cancer patients to radioactive iodine, we came across a very interesting fact. A 72-year-old patient had a single lesion, of thyroid origin, over the femur, and still had all of his thyroid. At the beginning, this case looked hopeless. The count over the thyroid was of the order of 14 mc, but that over the tumor was only 0.5 mc, after an oral dose of 40 mc. This

patient showed a rapid turnover of iodine over the thyroid, the activity decreasing to one-half in a couple of days. We thought that we could control at least the primary lesion by irradiating the surrounding thyroid tissue; namely, by cutting the blood supply.

We kept taking readings of him. Then an interesting thing happened. At about 15 days after the first dose, we gave 8 mc and we observed that the metastasis in the hip showed an increase in radioactivity but the thyroid did not. We could not believe this, so we tried again and obtained identical results. We had to conclude that we had affected the thyroid but not the tumor. While the thyroid weighed only a fraction of the tumor, it had picked up initially 50 times as much as the lesion, so that the concentration of radiation in the thyroid had been much higher than in the lesion. However, we decided that, since we had started with a ratio of 14 to 0.5 in favor of the thyroid and had ended up where a third dose had made the hip more radioactive than the thyroid, it was worth while to wait 60 days to see what would happen. The result was striking indeed. A fourth dose at the tracer level showed that while the thyroid had practically ceased to function, the metastasis had become much more avid for iodine, its uptake increasing from the initial 0.5% to 22%. Since soon after inactivation of the thyroid, the excretion of iodine increased while the tumor uptake remained practically constant, I am loath to believe that the subsequent increase in tumor uptake, after sixty days, is a result of lack of competition for the inorganic iodide on the part of the thyroid. It is much more likely that we had modified the capacity of the tumor to collect iodine and that the process could not be induced overnight. As a matter of fact, there was good reason to believe that the increase in avidity would have been greater or more rapid if the thyroid had been excised surgically.

Since then, several cases of metastasis responding to thyroidectomy (either surgical or by means of I^{131}) have been reported. Theoretically, surgical thyroidectomy is to be preferred on several points.

In conclusion, our experience with I^{131} has been that the radioactive element is capable of outstanding palliation in certain cases. In others it proves very disappointing; there remains, therefore, the problem of establishing criteria for selecting the cases which are apt to be benefited by it. I might mention, for instance, that the outstanding result on the first patient was attained with a tumor to blood dose ratio of 300 to 1, whereas in the second case, in which there was outstanding palliation, this ratio was 70 to 1. It seems desirable, therefore, to reach concentrations of the order of 100 or so. I should like to point out that the problem of finding means of concentrating radioactive isotopes in cancerous tissues is difficult. It is not likely that it can be done with inorganic compounds; the concentration of iodine in the thyroid is an outstanding exception. A method which looks promising is the one presented in 1943 by McClintock and Friedman, whereby, pneumococcus antisera were tagged with uranium. Two types of pneumococci were used and the specificity in uranium deposition was uncanny.

Dr. Pressman of Memorial Hospital tagged antimouse kidney serum with radioiodine and obtained deposition in the kidney. The specificity in deposition brought out by this method is excellent. It is too early to venture whether anything of this sort can be used against neoplastic tissue; it is, however, a hopeful approach in the field of cancer therapy and, in any case, a worthy subject to elucidate in the future.

THE NATURE AND THERAPY OF RADIATION SICKNESS

A. M. BRUES, M.D.*

A discussion of atomic warfare cannot be given in terms only of radiation. Many structures were destroyed by the blast alone, and many individuals were killed and injured by blast effects. We have seen the same crush injuries and trauma from flying debris, that we see in disasters of other types. The second phase of the atomic bomb injury is the heat. Burns from thermal energy were very frequently observed. This was due to infra-red radiation or was from energy of other wavelengths such as ultra-violet light. These lesions would clinically pass as "flash burns"; the differences between these and ordinary flash burns from gasoline being due to the fact that the distribution of burns on the body is that of heat coming from a point source, at some distance. You can line up such an individual in such a way that all of him which is seen from a given side is burned and all the rest of him is not burned.

The other thing about the thermal burns from these bombs is the fact that they often occurred according to the pattern of the clothing. Japanese wear clothing of bright colors and gay patterns, and where the clothing is white and reflects heat and light, burns are not seen at a critical distance, where if the clothing were dark, the heat would be absorbed and would burn. Keloids were commonly seen as late results of these burns.

We are not entirely certain whether the Japanese, like the American Negroes, are especially prone to develop keloids, whether the keloids are the particular consequence of flash burns, or whether the keloids develop because of the rigorous conditions and minimal medical care which existed after the catastrophies at Hiroshima and Nagasaki. In any case, many keloids were seen.

Differences in individual susceptibility were seen. In one of the junior high schools in Hiroshima, for example, there were about 200 boys standing in the schoolyard doing calisthenics. Japanese children usually do calisthenics at this time in the morning, and this particular group was facing the bomb. One saw all graduations from the slightest perceptible scar tissue under the skin with no visible skin changes to severe keloids in a group of individuals of the same age who had had an identical exposure. Many of the burned individuals remember exactly what they were doing at the moment of the blast, and can replace themselves in the positions which they held at the time of the explosion.

Blast injuries were the greatest cause of death in the bombed areas. Burns were the second cause of death; and radiation sickness was third, accounting for perhaps 10,000 to 25,000 of the deaths in Hiroshima. Acute radiation sickness is a state which is caused by radiation as from an atomic bomb, an overdose of x-ray, or from other sources of ionizing radiation to the whole body. The human lethal dose of x-ray is between 400 and 500 roentgen units. The amount which is used as total body radiation in the treatment of blood diseases such as leukemia and lymphoma may be as high as 100 r. In other words, this is a fair or at least a substantial proportion of the human lethal dose. If one is giving radiation locally to a radio-resistant tumor, then doses as high as several thousand roentgen units may be used, although, of course, this is only over a very small part of the body, so that the total energy absorbed is much less than in the case of the individual who gets total body radiation.

After irradiation, the individual develops, within one or two days, evidence of destruction of the blood forming organs. All types of circulating white blood cells are depressed. The only premonitory sign before this has been nausea, vomiting, and depression, which is characteristically seen in patients who have been treated with x-ray in heavy doses particularly over the abdomen. This first stage

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is not fatal except after extremely large doses of radiation, and lasts only a few hours. During the period of leukopenia, patients develop ulcerations in the mouth and intestinal tract and a bleeding tendency with a prolonged clotting time due, presumably, to the presence of material in the blood which increases the clotting time through a heparin-like action. As a result of ulcerations in the gastrointestinal tract, infectious organisms get into the body. As a result of the leukopenia, they are much more likely to yield to bloodstream infections so that these individuals have the various signs and symptoms of bloodstream infection, generalized and sometimes localized as well. As a result of this bleeding tendency, combined with the ulcerations in the GI tract, they may have bloody diarrhea. The fatal issue is sometimes more or less directly attributable to the bleeding tendency, on account of cardiac embarrassment due to hemorrhages into the myocardium or cerebral accidents due to hemorrhages in the central nervous system.

By the second month this acute radiation sickness, which ordinarily kills in the first few weeks, had passed off, and the only persons still dying as a result of the bomb radiation were dying in a subacute stage with aplastic anemia.

Falling of hair is commonly seen after total body irradiation; individuals who survived always had their hair return; that is, epilation was produced but this epilation was temporary. Dosages somewhat higher than the human lethal dose (for total-body radiation) will cause permanent epilation due to injury to the hair follicles. This would occur with perhaps twice the lethal dose. Some individuals were completely epilated over part of the head. These were people standing behind a protecting barrier, so that an area of epilation occurred in the unprotected region but the whole body did not receive a lethal dose of radiation.

Another effect brought about by radiation is, of course, sterility. Temporary sterility can, again, be produced in the male with an amount of x-ray or atomic bomb radiation which is not quite sufficient to cause death. The birth rate at Hiroshima went down for a period corresponding to about two months after the bombing. Although other factors were doubtless involved, radiation was suggested by the presence of aspermia, which was temporary. Again, with local irradiation over the gonads in higher dosages, permanent sterility can be produced. It requires still higher dosages to produce sterility in the female but when it is produced in the female it is generally permanent.

Over longer periods of time, chronic effects of radiation are manifest in various forms. Animals that receive doses of radiation insufficient to kill them (perhaps 20% or more of that dose) will have their life span defintely shortened. There can be no predictions about a given human or a given mouse but, the mortality curve is foreshortened. There is a higher tendency to develop tumors of all sorts. Mice are especially prone to lymphoma and lymphatic leukemia and they are more susceptible after radiation. Lymphoma can be induced almost universally in some strains of mice by giving them total body radiation in the order of 400 r. The same is true to a much smaller degree in man; radiologists have ten times as much leukemia as other individuals.

Local irradiation results in local cancer development. Radium and radiostrontium, for example, are deposited in the skeleton. This may result, in various species, in a strikingly higher incidence of bone tumors.

Insofar as treatment of radiation sickness is concerned, we do not know any very efficient way of restoring the white cells after an animal is irradiated. This is obviously one of the most important factors in the toxic picture. Leucopenia and its secondary effects on the production of immune bodies by lymphocytes, and presumably loss of the influence of the neutrophiles on bloodstream infection, may be responsible for fatal infection. Transfusion of leucocytes is useless. The aplastic anemia which develops later on can be treated by transfusions if the bone marrow is capable of recovery.

As for the bleeding tendency, it has been found that certain substances which

neutralize heparin also neutralize a heparin-like substance which appears in the bloodstream and is responsible, in part, for the bleeding tendency, of which toluidine blue is the most efficient. Dogs and a few patients have been kept from bleeding for a period of several days when this bleeding tendency was present, by administration of toluidine blue.

General supportive therapy, watching the patient for signs and symptoms and giving him general medical care is certainly a very important part of the treatment of radiation sickness, and I suspect that it can be very effective. The people at Hiroshima got essentially no general supportive therapy as 80% of the physicians were dead and the hospital was rendered useless. There were no communications as the city was on fire for days. Under these conditions supportive therapy was at a minimum. Many of these individuals could have been saved had they been under adequate medical care.

As to the therapy for infectious disease, we have good evidence that experimental animals given x-ray in doses which would otherwise kill them, up to perhaps 1½ or 2 times the fatal dose, will survive if they are given antibiotic therapy. In other words, the invasion of infections into the undefended bloodstream is a very important factor in the radiation sickness. There are certain measures which, apparently, will prevent radiation sickness from occurring if administered before the radiation is given. Dr. Patt, in our laboratory, has carried out experiments with the amino acid cysteine which is a reducing agent by virtue of its sulfhydryl group. One of the primary chemical effects of radiation on the body is to produce oxidizing-free radicals from water. This basic chemical effect of radiation is quite likely responsible for later effects. Mice treated with cysteine will survive 1000 r. of x-ray; whereas, without this pretreatment they would not survive more than 550 r. Administration of cysteine after radiation is valueless, even if it is given before symptoms appear. One can also precondition certain tissues so that they can stand radiation better. This can be done with respect to two systems that we know of. One is the erythropoietic system. Red cell formation can be stimulated by phenylhydrazine which causes an immediate and direct destruction of red cells. The individual recovers from the resulting acute anemia by making red cells at a greater rate than usual. It was discovered by Jacobson that if animals were made anemic by phenylhydrazine and then given x-ray, their recovery was better than if they had not been anemic. The regenerative process enabled them, in some way, to develop less anemia than they would have done otherwise. This observation shows, incidentally, that the most rapidly proliferating cells are not always the most radiosensitive ones.

In the case of the white blood cells, it has been known for some time that estrogens in relatively large doses in mice cause a depression in the neutrophilic leucocytes and that a recovery takes place beginning in a few days. The maximum recovery rate occurs in a week or ten days. It turns out that an animal will recover more rapidly from radiation sickness, if an estrogen is given a week or ten days before he is irradiated. At this time he is actively recovering from leucopenia, and he actually does better under those circumstances. Not only is the recovery from radiation leucopenia more rapid, but the survival is greatly enhanced. This effect is sufficient to save a large proportion of the animals given the critical lethal dose of x-ray. It now appears likely that the outlook for specific treatments for radiation sickness is promising.

A number of different forms of therapy are considered useful in the acute symptoms which occur immediately after x-ray. These palliatives, including vitamins and glucose, are apparently of some value in relieving the preliminary vomiting and depression immediately after radiation. They are of no use in the fatal radiation syndrome which occurs during the first two weeks after irradiation. The adrenal cortical hormones may be of some value, but conclusive evidence has yet to be presented.

I should like to say a few words about

sensitivity of cells. Certain cells are more sensitive to radiation than others. In therapy of malignant disease it is well known that the diseases of the blood forming organs (leukemias and lymphoblastomas), generally respond to much less radiation than do carcinomas and sarcomas, while some carcinomas and sarcomas are more sensitive than others. The same holds true in the case of the normal cells of the body, the cells of the blood forming organs being particularly sensitive. The rapidly proliferating epithelia are also especially susceptible to destruction by radiation. The sensitivity of the intestinal tract is a case in point, while muscle and nerve tissue are highly resistant. It is possible that the different sensitivities of tissues may help us to understand the basis of radiation damage. For instance, one thing which radiations do very efficiently is cause genetic mutations. Irradiation produces a distinct chemical effect at a particular point which is reflected in mutation when this point occupies a particular locus on a chromosome. One wonders if the same sort of thing may not be true when radiations produce cancer. According to the somatic mutation theory, cancer may be due to a mutation in a cell which causes it to change its characteristics just a little. While many normal tissues have the potentiality to grow under stress, most of them are usually quiescent. Cancer tissue appears to be restricted in its growth capacity; it ordinarily grows at a definite rate which is altered only under drastic conditions. This could be due to a very simple chemical change and it might be caused by a chemical mutation occurring in a single somatic cell. If one looks at cells of tissues which have been radiated it is clear that the destruction to chromosomes is very considerable. Chromosomes may be fragmented as the direct results of radiation, or the fragments may heal abnormally. The displaced fragments of chromatin may lose their identity, or they may interfere with the normal process of mitosis. If the damaged cell goes through several subsequent divisions, it is clear that the daughter cells may be unable to survive because of loss of some of the chromatin which contains the genes necessary for cell differentiation. Where a broken chromosome heals abnormally, the result may be a chromosome bridge which interferes with separation of the daughter cells. Where tissue has been heavily irradiated, as in the treatment of cancer, one sees dying cells and a few with huge nuclei, suggesting that imbalance of genic material has resulted, in some cells, in the loss of capacity for cell division.

These changes may account for destruction of tissue in general, and are certainly most strikingly illustrated in the case of tumors which have reached the point of regression several days after X irradiation. They may also account for the occasional production of a malignant cell in irradiated tissue.

The future task of irradiation research includes, on the basic level, understanding the relationship of the early chemical and cytological effects to the gross pathologic results; and on the practical level, therapy of the radiation syndrome in the light of its physiology.

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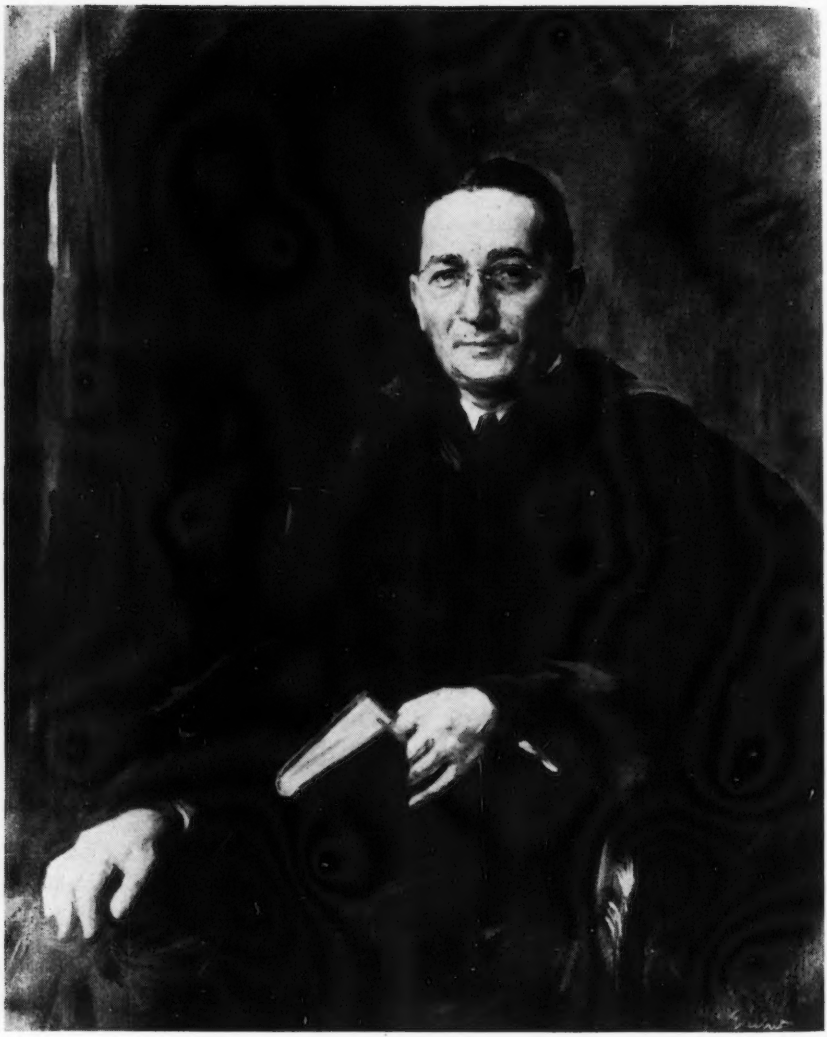

JOHN J. SHEININ, Ph.D., M.D., Sc.D.

President, The Chicago Medical School -:- 1950 —

"To have striven, to have made an effort, to have been true to certain ideals — this alone is worth the struggle."
— (From William Osler's "An Alabama Student.")

Portrait Presented by the Student Body, June 11, 1949

Esto Perpetua

Can there be any doubt in anyone's mind
That the greatest single event
In the history of The Chicago Medical School —
The denouement of the School —
Was complete approval and accreditation?

To you who were here before,
Dr. Sheinin's steady rise to the presidency of the School
Is a logical consequence,
As there is no honor
Which cannot justifiably be conferred
Upon our Dean.

It matters not the work involved
So long as HE HIMSELF does it; for
From the Chairman of the Board
Down to the last freshman student,
There is but ONE man for every job.

It takes only one meeting to know why . . .
In 1935, when Dr. Sheinin accepted the deanship
He had an idea.
Thirteen years later, when the idea was consummated,
There was the embryo of another idea.
Confident? Determined?
Why not?
But let us tell you about the president of a school
Who visited with the parents of a freshman student
To tell them their son was doing fine . . .
The president happened to be in their neighborhood . . .
They couldn't get over it . . .
And neither can we.

What about this other idea?
"We must first secure and consolidate what we have gained.
We shall contribute to the medical sciences
And I will accept nothing but a top-grade medical institution
For teaching and research.'
There will be a new school building;
There will be a research institute;
And there will be a graduate school with opportunities
For advanced degrees in the medical sciences.
This is not fantasy.
It will happen in my time.
It is because I believe in these things
That I felt it my duty to sacrifice teaching
And accept the Board's recommendation
That I become president of the School."

To you who came after
There would be little value in attempting to describe
Our feeling before accreditation
And the new hopes which have been given to us . . .
We came as derelicts;
We leave as princes.
We contributed the least;
We received the most.
Look at the portrait — at its color and texture —
No! Look at the Man . . .
And never forget that it was HIS ideas and ideals
That gave you your life and livelihood in Medicine.

And remember, too,
That the School can be a source of continuous pride
Or infinite sorrow;
Together we can bring to it
Honor and credit,
So that it may continue to serve
As a fountain of freedom
And a cathedral of learning.

CURRENT COMMENT

Opportunities in Public Health

Excerpt from a letter to Dr. Irwin S. Neiman from Dr. Charles F. Sutton, Chief, Division of Local Health Administration.

The fact that relatively few physicians are turning to careers in Public Health is explained chiefly by the fact that there have been, and still remain, much more lucrative opportunities in other fields. There is, however, a growing need for physicians especially trained in Public Health to staff full-time local, county or multiple-county Public Health Departments. If we are going to meet the demand, young men must begin entering this field from internships and from each of the classes now in medical school.

Two developments should affect this situation. Salaries have gradually edged upward for those physicians engaged in full-time Public Health careers. Salaries now compare reasonably well with net incomes of private practitioners of comparable competence. Secondly, there has been developed over the last three years a Specialty Board in Preventive Medicine and Public Health. This means that men entering this field now need not find themselves cut off from the possibility of entering a medical specialty. It means that the considerable amount of preparation, and experience required of those entering into Public Health work, is now appropriately recognized. It means that other employees of the medical profession will have more reason to properly recognize and respect their Public Health colleagues.

In order that at least a few medical students might have the opportunity of seeing public health activities at first hand, the plan of providing summer "Clerkships" in local public health departments was devised. The plan has been in operation for three years. Last year, for the first time, all five medical schools in Chicago were represented. We were very happy to see interest in this summer experience develop in this manner.

Money for this purpose is limited. Likewise, health departments which are in a position to expend the effort required to give medical students a good summer experience, are limited in number. Insofar as finances permit, this plan will continue, provided we learn before too long that satisfactory medical public health recruits are found in this manner. The number of students chosen from any one school will, as a rule, be proportional to the size of the respective student bodies. Where very few students can be taken, at least one will be chosen from each school if applications are received.

The summer work provided for students will be largely in downstate County Health Departments, for the reason that it is in this type of health department that the future needs will be greatest. Students will be given work in Epidemiology, Sanitation and at times in Administration. They will be given the opportunity to see the entire operation of the health departments. Where practicable, they will be given special projects to carry on in addition to the other work.

The successful Public Health Physician should have a deep interest in his chosen field, should be able to maintain excellent human relationships with those among whom he works, should be sufficiently competent to succeed in any other branch of medicine, should have a deep sense of responsibility to those whom he serves, should enjoy working as many and at such hours as may be required to accomplish his task, and ideally should have a flair for administration.

To be successful he must be able to win ready acceptance of himself as a person in the community where he is employed. Probably most important of all would be his ability to command the respect of his fellow physicians.

BOOK REVIEWS

THE PRACTICE OF UROLOGY. By Harry C. Rolnick, M.D., Professor and Chairman of the Department of Urology, The Chicago Medical School. Cloth. Complete in 2 volumes. 1245 pages with 1350 illustrations and 9 plates in color. J. B. Lippincott Company, Philadelphia, London, Montreal. 1949. $24.00.

This comprehensive and detailed treatise dealing with the diagnosis and treatment of urologic disorders can be considered a personal triumph for Dr. Rolnick. For the first time in many years the medical profession is able to fall back on a work which is not only genuinely accurate but one which is written in a style clear to all — from the student to the urologist. Presented in two handsome volumes, the textual material is extremely well-organized, first presenting the embryology, anatomy and physiology of the genito-urinary tract and then discussing the methods of accomplishing a complete and thorough urologic study. This includes a description of the various urologic instruments and their application. An excellent chapter on laboratory methods, written by Dr. Israel Davidsohn, clarifies the interpretation of urine studies and renal function tests.

In discussing some of the more common diseases of the urinary tract, Dr. Rolnick stresses the importance of early and accurate diagnosis. This will prove especially beneficial to the general practitioner who will now be able to make keener and surer diagnoses than heretofore. The section on kidney diseases is superb, notably the chapters on nephritis and nephrosis. Dr. Rolnick was ably assisted by Dr. Russell D. Herrold, Dr. Rubin H. Flocks, and Dr. David Presman who contributed scholarly chapters on chemotherapy, transurethral surgery, and post-operative complications in urology, respectively. The paper and print are excellent and the numerous illustrations are well-chosen. The Practice of Urology, written by one of the most noted men in the field, is highly recommended to the student, intern, resident, general man, and urologist. It should be in every medical library and will prove of inestimable value as a classic reference book on the subject of urology.

DISEASES OF THE HEART. By Charles K. Friedberg, M.D. Cloth. 1081 pages with 79 figures. Philadelphia and London: W. B. Saunders Company, 1949. $11.50.

Probably one of the most complete and thorough volumes on cardiac disease, this brand new book represents a great advance in the study and clinical evaluation of any and all the pathologic conditions referable to the heart. What is of particular interest and value is the special emphasis that Dr. Friedberg places on the pathologic physiology of cardiac disorders, including the pathogenesis or mechanism of the symptoms and signs of circulatory failure, of angina pectoris and myocardial infarction, and of the various manifestations of the individual cardiac diseases. The author explains that these discussions "are not exhibited for mere academic consumption, but with the belief that an understanding of the dynamic events responsible for clinical phenomena is essential for maximum skill in diagnosis and treatment." The text provides especially thorough coverage of the more commonly encountered disorders — heart failure, coronary disease, rheumatic fever and rheumatic heart disease. In addition, there is reference to the very recent advances in the surgical treatment of various clinical and experimental cardiac lesions including coronary artery disease, valvular disease and septal defects as well as other congenital anomalies, tumors and traumatic disturbances. Written in a manner clear to all, this text stresses the salient features of each condition and affords an excellent bibliography at the end of each of its 49 chapters. It is therefore enthusiastically recommended to all students, interns, practitioners, internists and cardiologists.

THE YELLOW EMPEROR'S CLASSIC OF INTERNAL MEDICINE. With an Introductory Study by Ilza Veith, M.A., Ph.D. Cloth. 253 pages with 24 figures. Baltimore: The Williams and Wilkins Company, 1949. $5.00.

This fascinating book is a translation of Chapters 1-34 of Huang Ti Nei Ching Su Wen, the oldest Chinese medical book extant, and presents the conversation between the Emperor, Huang Ti (who ruled China in 2697 B.C.) and his minister on medicine, ethics, religion, philosophy, and regimen of life. This classic has been the basis for all subsequent medical writing in China and Japan, and is still considered the outstanding

authority by Chinese orthodox medical practitioners. The reading is delightful and should prove extremely interesting to all those connected with the field of medicine.

NORMAL VALUES IN CLINICAL MEDICINE. By F. William Sunderman, M.D., Ph.D., and Frederick Boerner, V.M.D. Cloth. 845 pages with 237 figures and 413 tables. Philadelphia and London: W. B. Saunders Company, 1949. $14.00.

This unusual text is devoted exclusively to a discussion and compilation of values which may be termed "normal." It includes most every standard value that would be useful to those in the field of medicine, and as a reference work for such values is unexcelled. Some of its contents include normal values for the EKG, urine, liver function, blood elements, sedimentation rate, blood pressure, etc., as well as normal anatomical measurements for all parts of the body, data on the teeth and saliva, and many useful miscellaneous facts on food values, drugs and their dosages, and life expectancy at various ages. Altogether there are 845 pages packed full of information which, for the most part, will not appreciably change within the next few decades. It is especially recommended to the general practitioner.

AN ATLAS OF THE BLOOD AND BONE MARROW. By R. Philip Custer, M.D. Cloth. 321 pages with 288 illustrations, 42 in color. Philadelphia and London: W. B. Saunders Company, 1949. $15.00.

This new book, designed to promote greater accuracy in hematologic diagnoses, will be especially useful to clinical hematologists, pathologists and medical technologists. The first section is devoted to the development and normal function of hematopoietic tissues, while the latter part is primarily concerned with disorders of the blood and bone marrow. In almost all cases there is an attempt to correlate changes in the peripheral blood with those in the bone marrow. An abundance of superb high-power photomicrographs will be found throughout the text and these make possible direct comparisons with cells as actually seen under the microscope. While of no great import to the medical student or practitioner, it will be extremely valuable to those working in the field of hematology.

DISEASES OF METABOLISM. Edited by Garfield G. Duncan, M.D. Cloth. Second edition. 1045 pages with 167 figures. Philadelphia and London: W. B. Saunders Company. $14.50.

The purpose of this text is to "present the fundamental knowledge of metabolism, to apply this knowledge to the explanation of diseases of metabolism and to outline a rational basis for the treatment of these diseases." In attempting to fulfill this purpose, Dr. Duncan has been most wise in selecting a group of outstanding authorities to assist him in his work. The text is extremely well-organized and in addition to three excellent chapters on carbohydrate, protein, and lipid metabolism, contains all the fundamental principles governing the various metabolic dysfunctions as well as the diagnosis and treatment of each. This second edition, which was reprinted in 1949, was published in 1947; consequently, some of the newer work on the adrenal gland and its hormones is not discussed. The type, paper, and binding of the text is excellent, and it should prove quite valuable to the medical student and those interested in the metabolic disorders.

THE EYE AND ITS DISEASES. By 92 international authorities. Edited by Conrad Berens, M.D., F.A.C.S. Cloth. Second edition. 1092 pages with 436 illustrations, 8 in color. Philadelphia and London: W. B. Saunders Company, 1949. $16.00.

One of the most complete one-volume works on the eye and its diseases, the text covers every phase of the subject from embryology to laboratory diagnosis and legal aspects of ophthalmology. The material represents the contributions of 92 authorities on the subject and is thoroughly up-to-date. Accepted advances in therapeutics, especially as concerns the antibiotics have been carefully considered. Recent advances in the knowledge of eye diseases have been thoroughly reviewed and careful selection made of the material included in this new revision. The bibliographies appearing at the end of most of the chapters include the more recent references. While not of great value to the medical student or intern, it will, indeed, make an invaluable reference work and should, therefore, be included in the libraries of every practicing physician and ophthalmologist.

THE PHYSIOLOGICAL BASIS OF MEDICAL PRACTICE. By Charles Herbert Best, M.D., F.R.S., F.R.C.P., and Norman Burke Taylor, M.D., F.R.S., F.R.C.S., F.R.C.P. Cloth. Fifth edition. 1330 pages with 601 figures, 95 tables and numerous colored plates. Baltimore: The Williams and Wilkins Company, 1950. $11.00.

This monumental classic needs no euphuistic commentary from any source; the work speaks for itself. For many years "B & T" has been considered by medical students and teachers alike to be the epitome—the *ne plus ultra*—of physiology texts. It will undoubtedly remain so. The present edition has grown by more than 100 pages, many changes and revisions having been included. Among these latter are: shock, potassium balance in cardiac perfusion, renal function, anemia, endocrines, and more. The pages and print are good and the book is bound in a handsome green and gray cover. From the student's point of view, as well as for the clinician and research man, this is unquestionably the finest tome on the subject and is enthusiastically recommended to all.

THE ADRENAL GLAND. By Frank A. Hartman, Ph.D., and Katherine A. Brownell, Ph.D. Cloth. 581 pages with 72 illustrations. Philadelphia: Lea & Febiger, 1949. $12.00.

The adrenal gland and its homologues, including a study of all phases of interrenal and chromaffin tissue are considered in this enlightening work. It presents a comprehensive account of our knowledge of the adrenal gland, especially from the functional viewpoint, as determined by animal experimentation and clinical observation. Embry-

ology, morphology, histology and cytology are described; chemistry, physiology and pharmacology are treated extensively; and an account is given of the pathological changes in the gland and in the body when the gland is abnormal, with the clinical picture involved. Special reference is made to 17-hydroxy-11-dehydro-corticosterone (Compound E), now claiming the spotlight in recent medical research. Other subjects covered are Cushing's syndrome, the diagnosis and treatment of Addison's disease, and many more. Each chapter is epitomized by a summary at the close and there is an extensive 125-page bibliography. The binding and cover are superb, the paper and printing excellent and while of no special interest to the student or practitioner, this text should have wide appeal to the clinician, physiologist, pathologist, and endocrinologist.

HUMAN HELMINTHOLOGY. By Ernest Carroll Faust, Ph.D. Cloth. Third edition. 744 pages with 313 engravings. Philadelphia: Lea & Febiger, 1949. $10.00.

For the third edition of this practical work, Dr. Faust has thoroughly revised the text-matter to bring it in line with current knowledge on the subject. New material has been added on Anthelmintics and many other changes and additions have been made throughout. Thirty-four new illustrations have been added and some older ones revised and remodeled. The bibliography has been substantially increased and brought up-to-date. Dr. Faust has made this text an outstanding reference book for practitioners and research workers, as well as an ideal text-book for teachers in the field. Of the helminth parasites, each important species is considered for its historical background, structure, life cycle, geographical distribution, epidemiology, pathology, symptomatology, diagnosis, treatment, prognosis and control. In this most comprehensive work all the available information in the field has been correlated for the clinician, the sanitarian and the medical zoologist.

DISEASES OF WOMEN. By ten teachers under the direction of Clifford White, M.D., F.R.C.P., F.R.C.S. Cloth. Eighth edition. 461 pages with 170 figures. Baltimore: The Williams and Wilkins Company, 1949. $5.75.

Written in a very concise and lucid manner, this text covers virtually all the pathologic conditions to which the distaff side is heir. Each condition is described as to its etiology, pathology, signs, symptoms, diagnosis and treatment. The text is extremely well-organized; succinct, clear-cut, unequivocal facts are reported rather than any prolix detail. This makes the work especially useful for the medical student and intern, and will also be of great service to the general practitioner.

PAIN SYNDROMES. By Bernard Judovich, M.D., and William Bates, M.D. Cloth. Third edition. 357 pages with 181 illustrations. Philadelphia: F. A. Davis Company, 1950. $6.00.

The purpose of this monograph is to show that clinically, the interpretation of pain can be greatly facilitated by eliciting hyperalgesic or tender skin zones which accompany the pain. The authors base their work upon the fact that clinically, the combination of segmental pain and tenderness usually appears to be due to factors which irritate roots, ganglia, or trunks of the spinal sensory nerves, and not due to painful impulses originating in diseased viscera; in most instances, therefore, pain and segmental tenderness of skin appears to be of somatic origin rather than visceral origin. With this in mind the authors have stressed the clinical value of tenderness and have devoted much space to treatment by paravertebral nerve block. While of no immediate value to the medical student it will prove of interest to the intern and practitioner of medicine as well as to the internist.

TEXTBOOK OF HISTOLOGY. By Jose F. Nonidez, D.Sc., and William F. Windle, Ph.D., Sc.D. Cloth. First edition. 456 pages with 287 illustrations. New York, Toronto and London: McGraw-Hill Book Company, Inc., 1949. $6.75.

As an elementary text-book in microscopic anatomy, this new work fulfills all the requirements of a good teaching text by presenting in concise form the fundamental facts about the finer structures of the mammalian body, and emphasizing—as far as possible—the functional aspects thereof. The binding is sturdy, the paper heavy and glossy and the print is good. The numerous photographs and figures are clear and well-chosen. The book is recommended to those students engaged in the study of histology both in college and in medical school.

ARTERIAL HYPERTENSION. By Irvine H. Page, M.D., and Arthur Curtis Corcoran, M.D. Cloth. Second edition, 400 pages with 19 figures. The Year Book Publishers, Inc., Chicago, 1949. $5.75.

This book, which is intended to be of use to those who undertake the care of patients suffering from arterial hypertension, has been extensively revised to keep abreast of the current trends in the treatment of this disease. A chapter has been adde on the diagnosis and treatment of hypertension due to known or ascertainable causes. The new drugs under study, as well as a detailed account of pyrogen streatment in malignant hypertension, is thoroughly discussed. The book is extremely well written and is strongly suggested to those practitioners and internists interested in the field.

SCHOOL NOTES AND NEWS

FACULTY

We extend a hearty welcome to Dr. Kurt Stern in his appointment as Associate in Pathology of The Chicago Medical School.

Dr. Stern, a native of Vienna, received his Doctor of Medicine degree from the University of Vienna School of Medicine in 1933. Upon completion of his internship, Dr. Stern engaged in research at the Institute of Biochemistry, University of Vienna.

In 1938, Dr. Stern came to the United States and was awarded a Research Fellowship at New York University, Division of Cancer Research, Bellevue Hospital, and the New York City Cancer Hospital. He then was appointed Resident Physician at the Institute for the Study and Treatment of Malignant Diseases in Buffalo, New York.

In 1945, Dr. Stern was appointed Assistant Pathologist at Mount Sinai Hospital in Chicago and in 1949 was given the position of Assistant Director of the Mount Sinai Research Institute. On October 1, 1949, Dr. Stern was appointed Associate in Pathology of The Chicago Medical School.

Among other societies, Dr. Stern is a member of the American Society of Clinical Pathologists, American Association of Cancer Research, Society for Clinical Research, American College of Pathologists, and the New York Medical Society.

Another new addition to The Chicago Medical School faculty is Assistant Professor of Anatomy, Dr. Harold Koenig, to whom we extend our heartiest greetings upon his return to his alma mater.

Dr. Koenig, upon graduating from Rutgers in 1942, was elected to Phi Beta Kappa and was also awarded the Van der Poel prize in Bacteriology and Biochemistry. In 1943, Dr. Koenig entered The Chicago Medical School. While in The Chicago Medical School, he was awarded the Junior Scholarship and was Prosector in Anatomy for three years. At the same time he also attended the Northwestern University Graduate School, where in 1946 he was awarded the Master of Science degree in Neurology and was also admitted to Sigma Xi. Upon graduation from The Chicago Medical School in 1946, he entered Walther Memorial Hospital for his internship. Upon completion of his clinical training, he entered the University of Pennsylvania Graduate School, where he received his Ph.D. in Anatomy. In 1947, Dr. Koenig was ap-

pointed to the position of Instructor in Anatomy at the University of Pennsylvania School of Medicine, and upon the completion of his requirements for the Ph.D. degree, in 1948, was appointed Assistant Professor of Anatomy at the University of Pennsylvania School of Medicine.

Dr. Koenig is a member of the American Association for the Advancement of Science, the Society of Sigma Xi, the Philadelphia Physiological Society, and American Association of Anatomists.

It is with pleasure that we announce the appointment of Dr. Edward F. Rosenberg to the Staff of The Chicago Medical School as Assistant Professor of Medicine. Dr. Rosenberg comes to The Chicago Medical School bringing with him a wealth of research and clinical experience.

Upon graduating from the Jefferson Medical College in Philadelphia, he studied at the University of Minnesota where he received his M.S., and Ph.D. degrees. After completing his internship at St. Luke's Hospital in Bethlehem, Pennsylvania, he became a Fellow in the Department of Internal Medicine at the Mayo Clinic. In 1938, while still at the Mayo Clinic, he became First Assistant in Pathology, and in 1939 he became First Assistant in the Department of Medicine, Section on Rheumatic Diseases. In 1942, Dr. Rosenberg became Chief of the Arthritis Clinic of the Department of Medicine at Michael Reese Hospital of Chicago. During the war, as a member of the Army Medical Corps, he served at the Army Rheumatism Center and the Army and Navy General Hospital in Hot Springs, Arkansas. He now serves as a civilian consultant to the Surgeon General of the United States Army.

Dr. Rosenberg is nationally known for his work in the fields of arthritis and rheumatism. He is also famous for his research with cortisone and ACTH. He is a Fellow of the American College of Physicians, the American Medical Association, Vice-President (1948-49) of the American Rheumatism Association, President of the Chicago Rheumatism Society, Sigma Xi, Alpha Omega Alpha, and many other national clinical and research societies.

Dept. of Microbiology and Public Health

The Chicago Medical School has been awarded a grant in the amount of $3,000 by the American Cancer Society, it was announced recently. The grant, which was recommended by the Committee on Growth of the National Research Council, will be used for an investigation to determine the diagnostic value of cancer anti-antibodies under the direction of Dr. Irwin S. Neiman, Professor and Head of the Department of Microbiology and Public Health.

Dr. Neiman has recently been elected a Fellow of the American Public Health Association.

Dept. of Orthopedics

Dr. Donald Miller was awarded second prize for his exhibit on Vascular Complications in Orthopedics, at American Academy of Orthopedics.

Dept. of Dermatology and Syphilology

Dr. David M. Cohen has been elected to active membership of the Chicago Dermatological Society. Dr. Cohen is acting head of the Department of Dermatology and Syphilology.

ALUMNI NEWS

The State of California has amended their Medical Practices Act to include graduates of The Chicago Medical School who are veterans and who were residents of California before they entered medical school.

Class of 1941

Dr. John M. Staron has been re-elected secretary of the Jackson Park Branch of the Chicago Medical Society. He has also been appointed the assistant medical director of the Electro-Motive Division of the General Motors Company.

Class of 1943

Dr. and Mrs. Rudolph Bromberg proudly announce the birth of their daughter, Billie Joy, on December 29, 1949.

Class of 1944

Dr. Judd R. Breakstone announces the opening of offices for the practice of Gynecology and Obstetrics in Miami Beach, Florida.

Class of 1945

Dr. Seymour L. Gurchin was married on November 6, 1949, to Miss Sylvia Ruth Reman of Brooklyn, N. Y. Dr. Gurchin also announces the opening of his office at 1842 Bryant Avenue, Bronx, New York City.

Class of 1946

Dr. and Mrs. Andre Fiscella are to be congratulated on the birth of a daughter, Leslie Ann Susan, on March 22, 1949.

Congratulations to Dr. and Mrs. Edward B. Jaffe on the birth of William Warren on August 23, 1949.

It's a boy, Michael Jacob, born on September 13, 1949 to Dr. and Mrs. Louis Cholden.

Dr. Bernard Shulman, in collaboration with Drs. Frederick Steigmann, Hans Popper, and Roberta Hernandez has published an article "Flocculation Tests in the Diagnosis of Hepato-Biliary Disease" in *Gastroenterology* of July, 1949.

Class of 1947

Dr. Bernard Cutler announces the opening of his office for the practice of Medicine, Surgery and Obstetrics at 157 Hoyt Street, Brooklyn, New York.

Dr. Herbert Tetenbaum has opened his office for the practice of Medicine and Surgery at 1166 Eastern Parkway, Brooklyn, New York.

Dr. Samuel Weinberg announces the opening of his office at 65 Avenue D, New York, with practice limited to infants and children.

We wish to congratulate Mr. and Mrs. Leon Habin (Dr. Alice Ferris Habin) on the birth of their son Ronald Ian, on September 8, 1949.

Congratulations to Dr. and Mrs. Alex Norman on the birth of their daughter Beth Leslie on August 22, 1949.

Class of 1948

Dr. Patricia Jordan has been appointed to a residency in Psychiatry at the Elgin State Hospital.

The Alumni Association extends its heartfelt sympathy to the family and friends of these honored dead:

Dr. David Martin Rettinger of Chicago, Illinois.

Dr. James Leonard Paris, Sr., of Elizabethtown, Illinois.

Dr. Jordan Waldemar Rose, of Tucson, Arizona. Class of 1938.

STUDENT NEWS

Class of 1950

Congratulations to the Seymour Filmans on the birth of their son, and to the Leonard Graysons on the birth of their daughter.

Class of 1951

Congratulations are in order for Suzanne Allen who was married to Lee Widrow on June 25, 1949, and for Israel Siegel who was married to Mollie Danishefsky on September 7, 1949.

Lots of luck to Lawrence Berger and Beatrice Neuringer who became engaged in July, 1949.

Best wishes to Louis Kolokoff and Judy Rawson who were married on December 24, 1949.

Our best wishes and congratulations to those parents-to-be, the Bresslers, the Farbers, the Tokunages and the Udkoffs.

Class of 1952

Congratulations are in order to Mr. and Mrs. Arnold Tobin on their surprise marriage in Chicago in March, 1949.

To celebrate the completion of their pre-clinical courses, Arnold Scheinerman married Miss Edith Engel and Jack Behrman was wed to Miss Marilyn Deaner during the Christmas vacation.

Congratulations to Seymour Metrick and Miss Harriet Rubin of Chicago upon the announcement of their engagement.

NEW BOOKS IN THE LIBRARY

Albright & Reifenstein, Jr. Parathyroid glands and metabolic bone disease. 1948.

A.M.A. New and non-official remedies. 1949.

Behrens, C. F., ed. Atomic medicine. c1949. 2 copies .

Bast & Anson. Temporal bone and the ear. c1949.

Davidson, M. Diseases of the chest. 3d ed. 1948.

Goldzieher, M. A. Adrenals. 1929.

Jones, H. W., ed. Blakiston's new Gould dictionary. 1st ed. 1949.

Lemkau, P. V. Mental hygiene in public health. 1st ed. 1949.

Markowitz, J. Experimental surgery. 2nd ed. 1949.

Morrison, W. W. Diseases of the ear, nose and throat. c1948.

Mott & Roemer. Rural hygiene and medical care. 1st ed. 1948.

Patty, F. A., ed. Industrial hygiene and toxicology. 2nd vol. 1949.

Piney, A. & Hamilton-Peterson, J. L. Sternal puncture. 1949.

Rappaport, F. Rapid microchemical methods for blood and CSF examination. 1949.

Rich & Deardorff, ed. American foundations and their fields. 1948.

U. S. Serologic tests for syphilis. 1949.

Yearbook of General Medicine. 1949.

Advances in carbohydrate chemistry, vol. 4. 1949.

Addis, T. Glomerular nephritis. 1949.

Babkin, B. P. Pavlov, a biography. c1949.

Bailey, P. Intracranial tumors. 2nd ed. c1948.

Bauman, D. Diagnosis of pancreatic disease. c1949.

Biological preparations, vol. 1. c1949.

Cantor, M. Dynamics of learning. 1948.

Christopher, F., ed. Surgery. 5th ed. 1949.

Custer, R. P. Atlas of blood and bone marrow. 1949.

Doctoral dissertations, 1946-47. ed. by A. H. Trotler. 1947.

Elliott, G. M., ed. Film and education. c1948.

Ferris & Griffith, ed. The rat in laboratory investigation. 2nd ed. c1949.

Files, G. W. Medical radiographic technique. 3rd print. 1945.

Frey-Wyasling, A. Submicroscropic morphology of protoplasms. 1946.

Gaunt, R. Adrenal cortex. 1949. (N. Y. Acad. Sci., vol. 50, No. 6.)

Levine & Harvey. Clinical auscultation. 1949.

McNeill, C. Roentgen technique. 2nd ed. 1946.

Monographs on Surgery. 1950. Nelson & Sons.

Nickerson, J., ed. Biology of pathogenic fungi. 1947. 2nd copy.

Pepper, O. H. P. Medical etymology. 1949.

Recent progress in hormone research, vol. 4. 1949.

Sigerist, H. E. Medicine and health in the Soviet Union. c1947.

Smith, R. C. Guide to literature of zoological sciences. 1942-45.

Squibb & Sons. Curare. Introcostrine. 1946.

Thorn & Forsham. Diagnosis and treatment of adrenal insufficiency. c1949.

Tuft, L. Clinical allergy. 2nd ed. 1949.

Vesalius, A. The epitome. Translated by L. R. Lind. 1949.

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